WILSONS
Equity Research

Date
03 December 2021

Theme
Initiating Coverage

Company
EBR Systems Inc. (EBR)

O/W: When will major medtechs WiSE up?

We initiate coverage of EBR Systems at an OVERWEIGHT rating with a $1.50 12-month PT. EBR is a medical device developer pioneering ways to pace the left side of the heart without using wire leads. EBR's work immediately extends the rhythm management market by offering a solution for the 30% of patients who are untreatable. In the background, a second and potentially more powerful structural thematic is building. All global rhythm management peers are developing 'leadless pacing' for the right side of the heart but ignoring the left. They are creating a growing pool of leadless recipients who will ultimately need pacing on the left side of their hearts as well (most notably, those who develop heart failure). EBR's WiSE is the only technology that can 'upgrade' those patients without leads. We assess a US$1.06B TAM developing by 2025 in EBR's initial markets. Investigator-led research is taking WiSE into new indications including conduction system pacing. There are significant opportunities for indication expansion into *de novo* implants and difficult to treat populations with electrically blocked hearts and/or atrial fibrillation.

Recommendation	**OVERWEIGHT**
12-mth target price (AUD)	**$1.50**
Share price @ 03-Dec-21 (AUD)	$1.03
Forecast 12-mth capital return	46.0%
Forecast 12-mth dividend yield	0.0%
12-mth total shareholder return	**46.0%**
Market cap	**A$279m**
Enterprise value	**A$177m**
Shares on issue	**268m**
Sold short	
ASX 300 weight	n/a
Median turnover/day	$1.0m

Key points

Introducing EBR Systems. EBR pioneered the development of 'leadless pacing' for the left side of the heart. They did so because nearly a third of patients who qualify for cardiac resynchronisation therapy (CRT) either cannot be implanted with leads or whose leads fail to provide a benefit. The major rhythm management companies (Medtronic, Abbott, Boston Scientific) either couldn't do it (technologically challenging and associated with high clotting risks) or were not interested (believing that better lead design would solve the problems posed by leads). EBR implanted their first human patient in 2011, concluded a compelling feasibility study in 2016 and next year will report results from a pivotal trial. We model a US launch in 2024 and US$650M peak global sales.

Targeting a 2025 TAM profile of US$1B growing to US$2.5B. Our 2025 TAM estimate is split between two main categories: a) situations where conventional leads cannot or are not used (anatomical obstructions or high-risk patients); and b) patients where a conventional lead has been placed but is providing no benefit. Another US$400M in TAM stems from completely leadless CRT. Adding conduction system solutions for atrial fibrillation and bradycardia can get the WiSE TAM closer to US$2.5B.

Valuation. We have risked our $1.50/CDI target using discrete probabilities of clinical trial success (65%) and of commercial meeting or exceeding our forecasts (75%, if approved). Un-risked DCF is $2.35. M&A valuation scenarios suggest $2.50-$3.45 per CDI.

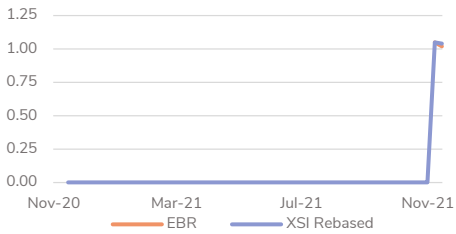
Risks and catalysts

Risks: a) regulatory approval risk; b) adverse reimbursement; c) slower than expected clinical adoption; d) intellectual property and competitive risks. **Catalysts**: a) SOLVE trial success; b) FDA approval; c) sales growth; e) adding sales territories; d) new indications.

Dr Shane Storey
shane.storey@wilsonsadvisory.com.au
Tel. +61 7 3212 1351

Dr Melissa Benson
melissa.benson@wilsonsadvisory.com.au
Tel. +61 2 8247 6639

12-mth price performance ($)



	1-mth	6-mth	12-mth
Abs return (%)			
Rel return (%)			

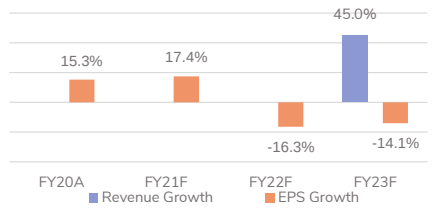
Earnings forecasts

Year-end Dec (USD)	FY20A	FY21F	FY22F	FY23F	FY24F
NPAT rep ($m)	-19.9	-18.7	-30.9	-36.3	-37.7
NPAT norm ($m)	-19.9	-18.7	-30.9	-36.3	-37.7
Consensus NPAT ($m)					
EPS norm (cps)	-12.0	-9.9	-11.5	-13.1	-12.5
EPS growth (%)	15.3	17.4	-16.3	-14.1	4.6
P/E norm (x)	-6.1	-7.3	-6.3	-5.5	-5.8
EV/EBITDA (x)	-5.7	-6.2	-3.9	-3.4	-3.3
FCF yield (%)	-9.4	-10.2	-15.8	-19.3	-20.1
DPS (cps)	0.0	0.0	0.0	0.0	0.0
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0
Franking (%)	0	0	0	0	0

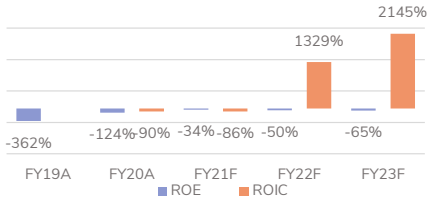
Source: Company data, Wilsons estimates, Refinitiv

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Growth rates



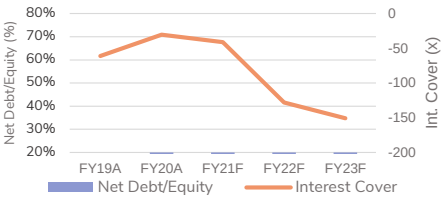
Returns



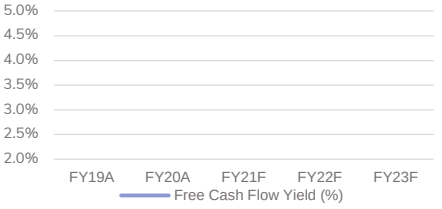
Margin trends



Solvency



Free cash flow yield



Interims (US$m)

	1H20A	2H20A	1H21A	2H21E
Sales revenue	0.0	0.0	0.0	0.0
EBITDA	-13.1	-6.6	-8.6	-9.4
EBIT	-13.2	-6.7	-8.7	-9.6
Net profit	**-12.9**	**-7.0**	**-9.0**	**-9.8**
Norm EPS	**-7.8**	**-4.2**	**-5.4**	**-4.5**
EBIT/sales (%)				
Dividend (c)	0.0	0.0	0.0	0.0
Franking (%)	0.0	0.0	0.0	0.0
Payout ratio (%)	0.0	0.0	0.0	0.0
Adj payout (%)	0.0	0.0	0.0	0.0

Key assumptions

	FY20A	FY21F	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F
Revenue Growth (%)	-76.9	171.3	-29.5	45.0	1,026.2	105.7	110.2	39.5
EBIT Growth (%)	-16.7	-8.4	67.5	17.7	3.8	3.1	-46.4	-99.5
NPAT Growth (%)	-15.3	-5.9	64.8	17.6	3.8	3.1	-46.1	-98.4
EPS Growth (%)	**-15.3**	**-17.4**	**16.3**	**14.1**	**-4.6**	**-7.5**	**-49.9**	**-98.6**
EBIT / Sales (%)	0.0	0.0	-2,552.5	-2,072.6	-191.0	-95.7	-24.4	-0.1
ROA (%)	**-45.4**	**-21.9**	**-59.6**	**-48.3**	**-101.5**	**-51.5**	**-43.8**	**-0.8**
ROE (%)	**-62.0**	**-24.0**	**-68.9**	**-54.6**	**-153.3**	**-63.7**	**-63.1**	**-1.2**

Financial ratios

	FY20A	FY21F	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F
PE (x)	-6.0	-7.3	-6.3	-5.5	-5.8	-6.2	-12.4	-871.3
EV/EBITDA (x)	-5.7	-6.2	-3.9	-3.4	-3.3	-3.3	-7.0	24.2
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FCF yield (%)	-9.4	-10.2	-15.8	-19.3	-20.1	-23.9	-13.5	-0.9
Payout ratio (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Adj payout (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Profit and loss (US$m)

	FY20A	FY21F	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F
Sales revenue	0.0	0.0	1.2	1.7	19.6	40.3	84.7	118.2
EBITDA	-19.7	-18.0	-28.8	-33.4	-34.0	-34.1	-16.0	4.6
Depn & amort	0.2	0.3	1.8	2.7	3.4	4.5	4.7	4.7
EBIT	**-20.0**	**-18.3**	**-30.6**	**-36.1**	**-37.4**	**-38.6**	**-20.7**	**-0.1**
Net interest expense	0.7	0.4	0.2	0.2	0.2	0.2	0.2	0.2
Tax	-0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Minorities/pref divs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Equity accounted NPAT	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit (pre-sig items)	**-19.9**	**-18.7**	**-30.9**	**-36.3**	**-37.7**	**-38.8**	**-20.9**	**-0.3**
Abns/exts/signif	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reported net profit	**-19.9**	**-18.7**	**-30.9**	**-36.3**	**-37.7**	**-38.8**	**-20.9**	**-0.3**

Cash flow (US$m)

	FY20A	FY21F	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F
EBITDA	-19.7	-18.0	-28.8	-33.4	-34.0	-34.1	-16.0	4.6
Interest & tax	0.0	0.3	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
Working cap/other	2.2	-1.3	-0.4	-2.5	-3.2	-10.4	-9.1	-6.0
Operating cash flow	**-17.5**	**-19.0**	**-29.5**	**-36.1**	**-37.5**	**-44.7**	**-25.3**	**-1.6**
Maintenance capex	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Free cash flow	**-17.5**	**-19.0**	**-29.5**	**-36.1**	**-37.5**	**-44.7**	**-25.3**	**-1.6**
Dividends paid	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Growth capex	-0.3	-1.1	-3.4	-3.5	-3.7	-4.2	-5.0	-5.0
Invest/disposals	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Oth investing/finance flows	-0.1	0.0	0.0	-3.9	0.0	-5.1	0.0	0.0
Cash flow pre-financing	**-17.9**	**-20.1**	**-32.9**	**-43.5**	**-41.2**	**-54.0**	**-30.3**	**-6.6**
Funded by equity	19.7	97.0	0.0	65.0	0.0	85.0	0.0	0.0
Funded by debt	-3.2	-0.1	-2.9	-1.6	-0.8	-0.8	-0.8	-0.8
Funded by cash	1.4	-76.8	35.8	-19.9	42.0	-30.1	31.1	7.4

Balance sheet summary (US$m)

	FY20A	FY21F	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F
Cash	1.2	82.7	46.9	66.8	24.8	54.9	23.8	16.4
Current receivables	1.4	0.1	2.0	2.0	3.2	4.0	5.0	10.0
Current inventories	0.7	0.0	0.0	0.7	1.3	4.0	4.0	1.0
Net PPE	0.9	1.3	2.3	4.3	6.4	8.9	11.4	13.9
Intangibles/capitalised	37.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total assets	**43.9**	**85.4**	**51.8**	**75.2**	**37.1**	**75.5**	**47.8**	**44.9**
Current payables	4.6	0.7	1.3	3.0	5.0	7.0	3.6	4.3
Total debt	0.0	3.6	0.0	0.0	0.0	0.0	0.0	0.0
Total liabilities	**11.8**	**7.4**	**7.0**	**8.8**	**12.6**	**14.5**	**14.7**	**15.4**
Shareholder equity	**32.1**	**78.0**	**44.8**	**66.5**	**24.6**	**60.9**	**33.2**	**29.5**
Total funds employed	**32.1**	**81.6**	**44.8**	**66.5**	**24.6**	**60.9**	**33.2**	**29.5**

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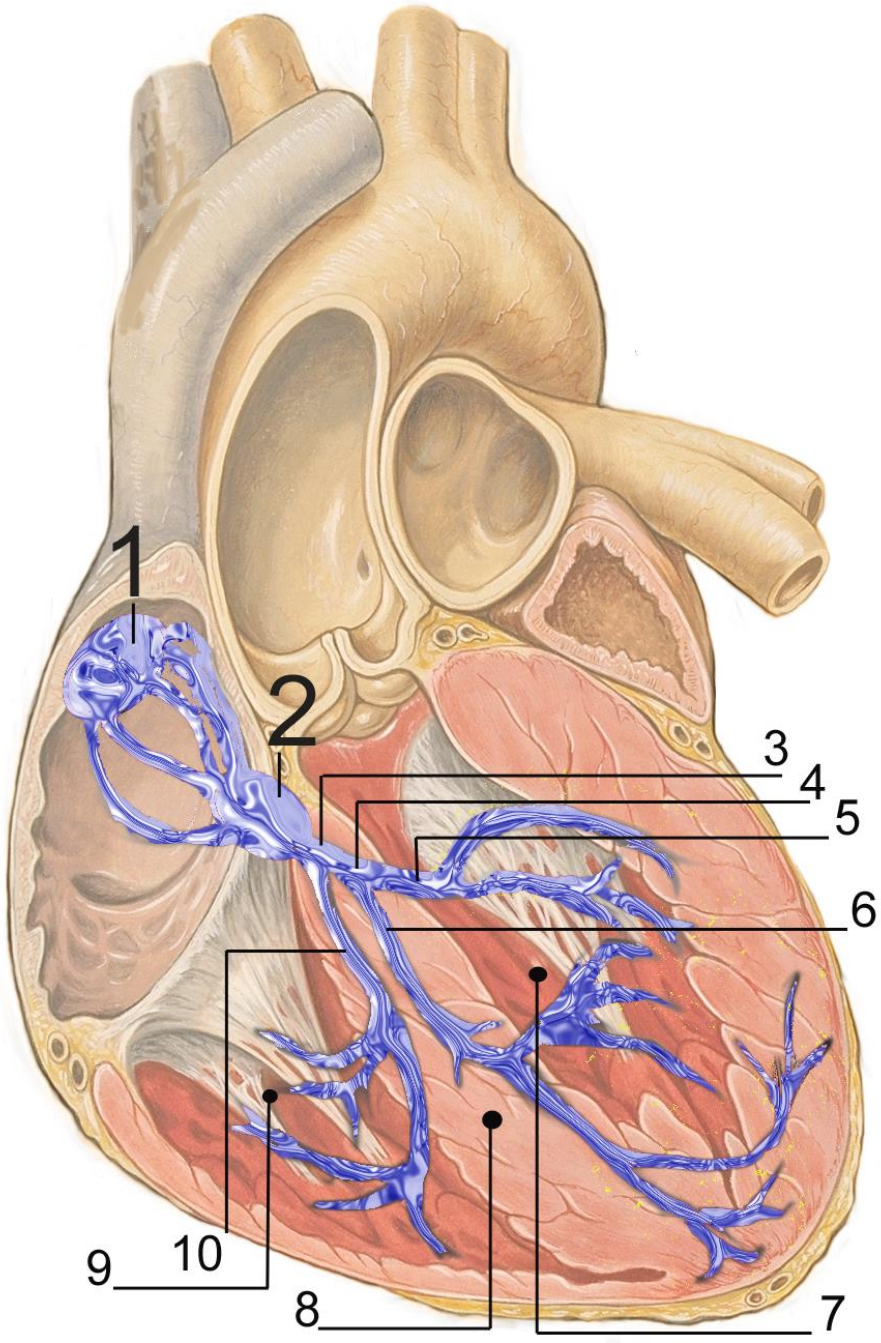
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Glossary

Acute lead failure	Patients who have an indication for CRT but who are unable to have the lead implanted on account of their anatomy or disease condition.
Atrial fibrillation (AF)	AF is a type of cardiac arrythmia characterised by rapid, irregular heartbeats. AF reduces the heart's pumping efficiency and increases the risk of clot formation and strokes.
Arrhythmia	A set of medical conditions characterised by problematic heart rhythm. In tachycardia, the heart beats too rapidly. In bradycardia, too slowly.
Atrioventricular (AV) node and AV block	The AV node is part of the heart's conduction system that co-ordinates the top of the heart and electrically connects the atria and ventricles. Patients with an AV block may develop abnormal heart rhythms.
BIVP	Biventricular pacing (BIVP) is synonymous with CRT.
Chronic lead failure	Patients implanted with a CRT device who have had their coronary sinus lead switched off. This category also includes patients whose CRT lead has become ineffective.
Conduction system pacing	A pacing strategy where a medical device stimulates the conduction system directly instead of peripherally via the heart walls.
Coronary sinus	The coronary sinus is a group of veins on the posterior surface of the heart that delivers blood to the right atrium. Conventional CRT places a lead in this vein to access the outer surface of the left ventricle.
CRT	Cardiac resynchronisation therapy is achieved by implanting a specialised pacemaker. In addition to the standard pacemaking leads implanted in the right atrium and right ventricle, a CRT has a third lead implanted in the left ventricle. The aim of CRT is to co-ordinate the left and rights sides of the heart to restore the heart's normal pumping action.
CRT-D	Defibrillator with cardiac resynchronisation therapy.
CRT-P	Pacemaker with cardiac resynchronisation therapy.
CRT non-responder	A patient implanted with a CRT who receives no clinical benefit despite the system functioning normally.
CRT upgrade	Patients who have been previously implanted with a pacemaker or ICD who develop a requirement for left ventricle pacing. The addition of a 'third' lead to provide CRT is considered an 'upgrade'.
Defibrillator	A medical device designed to deliver a dose of electric current to the heart to 'shock' it out of life-threatening arrhythmias.
De novo CRT	Patients with a CRT indication who receive the 3-lead pacing system as their first intervention.
ECG (or EKG)	Electrocardiography is a diagnostic tool that detects heart abnormalities by measuring the electrical activity as the heart contracts.
Electrical remodelling	The restoration or improvement in the heart's electrical conduction in response to therapy.
His bundle	The His bundle is a collection of electroconductive heart muscle cells that forms part of the heart's conduction system. It transmits impulses from the atrioventricular node to the right and left bundle branches, which in turn, are conduits by which the ventricles are activated.
ICD	An implantable cardioverter defibrillator is a medical device that detects and terminates fast heart rhythms (ventricular tachyarrhythmias). ICDs deliver high energy shocks that return the heart to normal rhythm and are lifesaving.
LBBB / RBBB	Left bundle branch block (LBBB) is a fault with the heart's central conduction system. In LBBB the electrical impulses do not travel efficiently to the left ventricle leading to a lag in contraction. Right bundle branch block (RBBB) impacts the right ventricle in a similar way.
LBBAP	Left bundle branch area pacing is a form of conduction system pacing. Leads or electrodes are placed in or near the left bundle branch to provide a more physiologically authentic activation pattern.
LV	Left ventricle is one of the heart's four chambers.. It is responsible for pumping oxygenated blood to the body.

LVAD	Left ventricular assist device. A medical device used to take over the circulatory function of the failing heart. LVADs are indicated in end stage heart failure patients as a 'bridge' therapy while they wait for a heart transplant.
LVEDV	Left ventricular end-diastolic volume – the volume of blood in the left ventricle before it contracts and ejects blood to the circulatory system.
LVEF	Left ventricle ejection fraction is the percentage of blood volume that is ejected from the left ventricle on a single contraction.
LVESV	Left ventricular end-systolic volume – the volume of blood in the left ventricle at the end of a contraction, before it refills.
NYHA Classification	New York Heart Association classification is a frequently used assessment of a patient's symptoms while performing physical activities. There are four levels of increasing severity: Classes I-IV.
Pacemaker	A pacemaker is a medical device that generates and delivers electrical impulses to the heart muscle chambers in an effort to co-ordinate their action. Regulating the heart's electrical conduction can restore natural rhythm and pumping action.
QRS complex	The QRS complex is the central and most visually obvious part of the heart's waveform, as seen on a typical electrocardiogram (ECG or EKG). It corresponds to the depolarization of the right and left ventricles of the heart and contraction of the large ventricular muscles. QRS is actually a combination of three waves: Q, R and S.
QRS duration (QRSd)	The time that elapses from the start of the Q-wave to the end of the S-wave in a QRS complex. In healthy adults the QRS duration is 80-110 milliseconds.
Remodelling	Changes in the heart's size, mass, geometry and function in response to injury.
Reverse remodelling	The partial reversal of cardiac remodelling as a response to therapy.
RV	Right ventricle is one of the four chambers of the heart. It pumps deoxygenated blood to the lungs.
VVI or VVI(R)	VVI or VVI(R) is one of the more commonly used pacing strategies. This mode of pacing prevents ventricular bradycardia and is primarily indicated in patients with atrial fibrillation with a slow ventricular response.

The Cardiac Conduction System



1. Sinoatrial node
2. Atrioventricular node
3. His bundle
4. Left bundle branch
5. Left posterior fascicle
6. Left anterior fascicle
7. Left ventricle
8. Ventricular septum
9. Right ventricle
10. Right bundle branch

1. Investment overview

1.1 Investment thesis

We initiate coverage of EBR Systems at an OVERWEIGHT rating with a $1.50 12-month PT. EBR is a medical device developer pioneering ways to pace the left side of the heart without using wire leads. EBR's work immediately extends the rhythm management market by offering a solution for the 30% of patients who are untreatable. In the background, a second and potentially more powerful structural thematic is building. All global rhythm management peers are developing 'leadless pacing' for the right side of the heart but ignoring the left. They are creating a growing pool of leadless recipients who will ultimately need pacing on the left side of their hearts as well (most notably, those who develop heart failure). EBR's WiSE is the only technology that can 'upgrade' those patients without leads. We assess a US$1.06B TAM developing by 2025 in EBR's initial markets. Investigator-led research is taking WiSE into new indications including conduction system pacing. There are significant opportunities for indication expansion into de novo implants and difficult to treat populations with electrically blocked hearts and/or atrial fibrillation.

Five key points supporting our OVERWEIGHT call on EBR Systems:

- **EBR satisfies our first rule of medical device investing: *just because one can, does not always mean one should***. EBR's WiSE system **can** provide cardiac resynchronisation therapy (CRT) for heart failure patients without using wires or leads to electrically stimulate the left ventricle. They achieved this by designing a tiny electrode that can be implanted inside the left ventricle and be powered wirelessly using an ultrasound transmitter. EBR **should** do this too, because up to 30% of heart failure patients who deserve CRT do not get it because they either cannot be fitted with wire leads or those leads fail. EBR's global peers have seemingly ruled the left ventricle as "too hard" a place to do business in. EBR can win in the left ventricle.
- **Clinical evidence reaching a crescendo over the next 12 months**. In **Appendix A3** we provide our review of EBR's peer reviewed clinical trial data. The totality of the data shows that WiSE restores the benefits normally associated with CRT but in patients who are ineligible, non-responding or otherwise failed. EBR is enrolling a pivotal, PMA-directed clinical trial (SOLVE-CRT). Interim data are expected this time next year setting up a potential FDA approval in late 2023.
- **Large TAM with FDA Breakthrough Designation (BDD) underwriting market access**. We assess an immediate pool of 50,000 patients in the USA in 2025 for whom WiSE will be the CRT modality of choice, if approved. WiSE's breakthrough status is likely to confer strong pricing, including a new technology add-on payment to incentivise early clinical adoption. Our view is that the availability of an FDA approved device with attractive Medicare payment will see cardiologists/electrophysiologists abandon experimentation in these patients and adopt WiSE. The patient groups EBR will target are those that are ineligible for conventional CRT and those in whom conventional and/or quadripolar transvenous leads have failed.
- **The major medtech rhythm management franchises cannot do what EBR does**. Neither Medtronic, Boston Scientific nor Abbott have any leadless CRT solutions in development for the left side of the heart. All are instead trying to improve the design of their leads. Counter-intuitively perhaps, all three are developing leadless pacemakers for the right side of the heart. In so doing they're creating a pool of pacemaker recipients who will inevitably need CRT – becoming an uncontested market for WiSE.
- **Solid valuation support behind our O/W call – real options provides key insights on potential M&A**. EBR has obvious corporate appeal because its lead asset is universally attractive to the three logical players and is set to grow (not cannibalise) the CRT market. Real options analysis shows that potential suitors could pay up to A$500M for EBR pre-FDA approval (2022-3) and A$1.2B post-approval (2024-5). M&A is the most likely mechanism by which EBR's value will crystallise. We have set risked DCF $1.50 as price target but un-risked $2.35 per CDI guides our choice of recommendation more.

1.2 Investment merits

- **EBR's WiSE CRT targets a large and immediately addressable population of untreatable heart failure patients.** We assess that in 2025 there will be over 75,000 HF patients that should receive CRT based on their clinical status and insurance eligibility but they will go untreated. In 60% of cases the implant procedure will not be successful because the patient's anatomy will not allow it or their risk-status as a patient will preclude the placement of wire leads to their hearts. The other 40% will have a CRT system installed in their chests but receive no benefit from it, due to chronic lead failure. If WiSE CRT could be made available to these patients as an alternative it would grow the global CRT market by over 30% that year. We assess that this untreated portion of the market represents a US$980M net sales market for WiSE in 2025 (global basis).
- **Well-developed evidence base culminating in pivotal trial results next year.** EBR's prospective trials and real-world data to date make the following clinical point: WiSE recipients can expect to receive similar efficacy benefits to those enjoyed by patients successfully treated with conventional CRT. Trials conducted in CRT non-responder and lead failures compare well with the foundational CRT studies of the early 2000s. Although non-randomised and uncontrolled, the trials show convincing evidence of biventricular pacing and objective improvements in heart structure and symptoms. EBR is completing the third and final phase of a pivotal trial with both RCT (sham-controlled) and single-arm components (SOLVE-CRT). Interim data next year could form the basis for marketing authorisation in USA.
- **US market introduction gets a potential tailwind from FDA Breakthrough status.** WiSE is eligible for reimbursement settings that encourage its adoption in both hospital (inpatient) and ambulatory (outpatient) settings for the first 2-3 years of launch.
- **Lack of organised competition in these initial CRT-refractory patients**. To the best of our research efforts we can find no evidence or physician feedback suggesting that Medtronic, Abbott or Boston Scientific have R&D programs trying to emulate what WiSE is achieving in the left ventricle. Instead, these companies appear to be relying on new lead designs. Our view is that the availability of an FDA cleared device with good safety, efficacy and product-specific reimbursement is a compelling advantage for EBR.
- **European jurisdictions already approved and enabled by the SOLVE-CRT data catalyst.** WiSE has been CE Mark approved since 2015. EBR's activities in Europe have been more directed towards market development, securing reimbursement and investing in technology development. Europe has been a testing ground for EBR's training programs and clinical filed support to ensure smooth adoption when the product is launched more aggressively following the release of pivotal trial data in late 2022.
- **Broad key opinion leader collaborations to expand EBR's leadership in endocardial left ventricular pacing**. EBR have a number of quality investigator led studies underway or in preparation. As the first pacing electrode that can be placed inside the left ventricle without obvious thrombosis risk, WiSE has captured the field's imagination. LV endocardial stimulation is thought to provide a more physiologic pattern of cardiac stimulation, and is thought less likely to induce arrhythmias and further deterioration (yet to be proven). The idea of using the WiSE electrode for conduction system pacing offers material indication expansion opportunities for patients that fall outside traditional CRT eligibility. Important groups include those with electrically 'blocked' hearts, bradycardia and heart failure patients with permanent atrial fibrillation. We assess that indication expansion can support ~2.5X the initial CRT-related TAM for WiSE (~US$2.5B).
- **In the background, the leadless pacemaker market creates a recipient 'upgrade' pool that only WiSE can serve**. Approximately 25% of all CRT sales today treat patients who already have a pacemaker for the right side of their heart but subsequently need their left ventricle paced as well. All major manufacturers are developing pacemakers that are free of transvenous leads. We estimate that this recipient pool will grow to 500,000 patients at maturity. Investigators have already published case studies showing that WiSE can be implanted to achieve completely leadless CRT for these patients. An investigator-led trial, sponsored by EBR, is expected to launch in 2022 to investigate this prospectively.

- **Obvious corporate appeal.** The natural owner of EBR is more likely the global cardiac rhythm management majors: Medtronic, Abbott or Boston Scientific. These entities can give WiSE the global marketing and medical support it needs. Importantly, WiSE stands to add to each of these businesses in the same way: exclusive position on the CRT-refractory patient group and integration with their burgeoning leadless pacemaker aspirations.
- **Successful ASX acquisition predicate recalled.** The cardiovascular medical device market more often builds new franchises via acquisitions. In recent years this trend has been obvious in heart failure (both interventional and monitoring), electrophysiology and transcatheter aortic valve replacement (TAVR). The EBR Systems situation bears similarities to that of HeartWare (HIN:ASX) which triggered two M&A events in the heart failure space. HeartWare's miniaturised left ventricular assist devices (LVADs) could be implanted without a median sternotomy and stood to significantly expand the market by bringing higher risk patient groups into implant candidacy.
- **OVERWEIGHT recommendation driven primarily by M&A optionality.** We have set our initial 12-month price target at $1.50/CDI which is our risked DCF valuation. The use of risked valuation is appropriate given EBR is still a year away from its key catalyst (FDA approval) and 60% of the stock sits in 12- or 24-month escrow, creating potential headwinds. Our fundamental view on EBR valuation is to consider it on an un-risked DCF basis (A$2.35/CDI noting that an acquirer's view on project risk is often better informed that those of generalist market investors) and/or the results of our M&A pricing analysis (up to A$3.45). Demand for the stock could be relatively subdued over its first 12 months of ASX listing. That makes setting 12-month price targets challenging but also creates good opportunities to accumulate EBR stock at a discount.

Medtronic ultimately acquired HeartWare for US$1.1B in 2016 which was in line with our un-risked DCF.

1.3 Investment risks

- **SOLVE-CRT trial evidence to drive US regulatory strategy and clinical adoption elsewhere**. To date, EBR has assessed the performance of WiSE CRT in small, prospective studies without randomisation or valid (sham) controls. Real world data is also available but with limited follow-up (6 months). Whilst results were supportive of CE Mark, evidence quality as it stands is too low to drive clinical adoption. The company's SOLVE-CRT trial began with the intention of being a 350 patient, randomised, controlled trial. COVID-19 disruption led to the trial being redesigned with both randomised controlled (n=108) and prospective, single-arm (n=192) components. The trial is being conducted under a revised Investigational Device Exemption (IDE) with clear safety and efficacy targets. We believe this study is of sufficient quality to support FDA approval and stimulate broader adoption in other markets.
- **Planned launch timing assumes success on an interim analysis.** The third and final part of EBR's SOLVE trial is recruiting now and could implant as many as 192 patients as per the IDE. EBR is planning a pre-specified interim analysis at 75 patients and is confident that this early data point will support an approval. If a judgement is made that the additional 117 patients are necessary this will delay the US regulatory pathway milestones by at least a year.
- **Room for improvement with WiSE and its ancillary deployment technologies**. We note that EBR is already moving to improve WiSE's battery life and provide a rechargeable option. The labelling describes battery life as 4-5 years. This can be shortened to 1 year if the distance between the ultrasound transmitter and the endocardial electrode is too far or if the patient's heart requires a stronger stimulus to activate. Technologies for catheter deployment are always improving. There is an opportunity to optimise the techniques used and sequencing of transmitter and electrode positioning.
- **Changing clinical practice is always difficult.** WiSE CRT is seeking to change engrained habits among electrophysiologists and other physicians. Common barriers to adoption include understanding new evidence and reluctance to undergo training for new procedures where complications are potentially life threatening. Anecdotal feedback suggests the learning curve with WiSE is short with complication rates no worse than those reported for leadless pacemakers.
- **Major medtech peers may dismiss WiSE as unnecessary.** Electrophysiologists are assessing alternative pacing strategies as solutions to CRT non- and sub-responsiveness but retro-fitting available leads for this purpose. Organised competition in EBR's targeted indications appears to be relatively low. It is difficult to establish whether major manufacturers have any interest in the unmet need. Efforts seem limited to lead design and perhaps innovation in CRT pacing algorithm design. It is not clear what one should conclude from none of the major manufacturers having leadless solutions for the left ventricle in development (i.e. too difficult or just unimportant?).
- **Payer risk**. WiSE CRT currently has very limited reimbursement support in Europe and none in USA. FDA breakthrough device status does confer pricing and reimbursement advantages for 2-3 years post launch. In the background, EBR must work towards Category 1 CPT codes and product-specific reimbursement. Delays in or failure to achieve coding, coverage and payment would have a negative impact on sales forecasts.
- **Low sales visibility in the short term**. WiSE received CE Mark over six years ago but EBR has not developed meaningful sales. The EBR prospectus indicates a US$26.8M investment in sales and marketing but shares no outlook for European sales.
- **Product risk**. A product recall or material safety issue with WiSE CRT could damage EBR's reputation as a medical device manufacturer. A product recall could result in a steep decline in sales, significantly higher expenses and potential exposure to litigation.
- **Reliance on others**. EBR relies on other suppliers and manufacturers for critical components including the receiver electrode (CIRTEC Medical Systems[1]) and other custom components (Micro Systems Engineering[2] and Nextern Innovation[3]).

[1] http://cirtecmed.com/
[2] https://www.mst.com/MSTgroup/mse
[3] https://nextern.com/

- **Intellectual property risks**. We review EBR's patent portfolio in **Appendix A5**. We provide no view or analysis on the scope, validity or enforceability of EBR's granted claims. Likewise, we have not done any work to assess freedom to operate. Whilst EBR's granted patents have expiry dates ranging from 2025-2033 patent term extensions are potentially available. We also note new provisional patents with filing dates of 2020 and 2021 which may extend into the 2040s if successfully prosecuted.
- **Access to development capital**. Our forecasts see the necessity for future equity capital in the event that EBR Systems elects to launch WiSE in the US market as an independent organisation. Our valuation is pre-emptively diluted for future equity raising(s). This entails assumptions on our part with respect to the availability, pricing and structure of such transactions. If EBR elects to enter markets in collaboration with others or via licensing/acquisition there is upside to our valuation.
- **Low liquidity in the ASX-listed EBR CDIs**. Approximately 60% of the CDIs on issue will not be listed for trading. In the absence of material revenue, periods without regular and authentic value catalysts could lead to low trading levels and demand for the stock.
- **Escrow headwinds**. As at the ASX listing date, 170.7M CDIs (>60% of the register) are subject to ASX or voluntary escrow with release dates extending to 2023. Approximately 4.6M shares may be released in February 2022. A further 46.1M CDIs are released 12 months following IPO. A further 120M CDIs are released 24 months post-IPO. Escrow events can create potential 'overhangs' and impede share price performance in a way that can be exacerbated by slower than expected progress by the business.

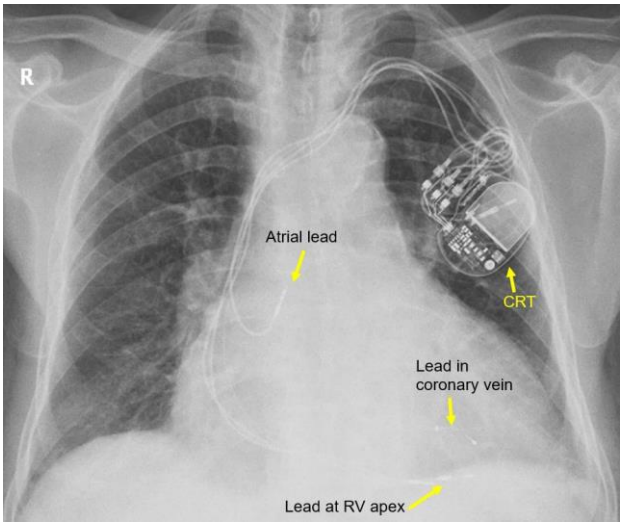
2. Company Overview: EBR Systems

2.1 History

Pacing leads were the key problem to solve for. EBR systems originated in 2003 with the mission of developing a cardiac rhythm management (CRM) solution that could avoid the use of leads (**Figure 1**). The CRT segment of the rhythm management market was only new at the time but it was already known that a significant number of eligible patients could not be implanted with leads or had suboptimal responses to lead-driven pacing. EBR was co-founded by Dr Debra **E**cht, Dr Axel **B**risken and Richard **R**iley. Echt was an experienced cardiac electrophysiologist (Stanford, Vanderbilt). Brisken was a medical physicist who had been part of the team that developed the first cardiac ultrasound scanner with GE Healthcare. Riley was a medical device R&D executive, previously at Cardiac Pathways Corp that was taken out by Boston Scientific. This team designed the first WiSE device and progressed it to a first-in-man study in 2011 (**Figure 2**).

EBR were not alone in the 'leadless pacing' pursuit. All major rhythm management companies were simultaneously developing leadless devices to pace the right side of the heart. EBR remains the only company to have achieved leadless pacing in the left ventricle. Introducing any permanent device hardware to the left ventricle is associated with very high risks of blood clotting. The challenge was to develop a miniaturised device that reside in the left ventricle and pace the heart wirelessly.

Figure 1. A conventional CRT system runs three leads from a subcutaneous, implanted pulse generator to a) the right atrium; b) right ventricle; and c) outside the left ventricle, via the coronary vein.

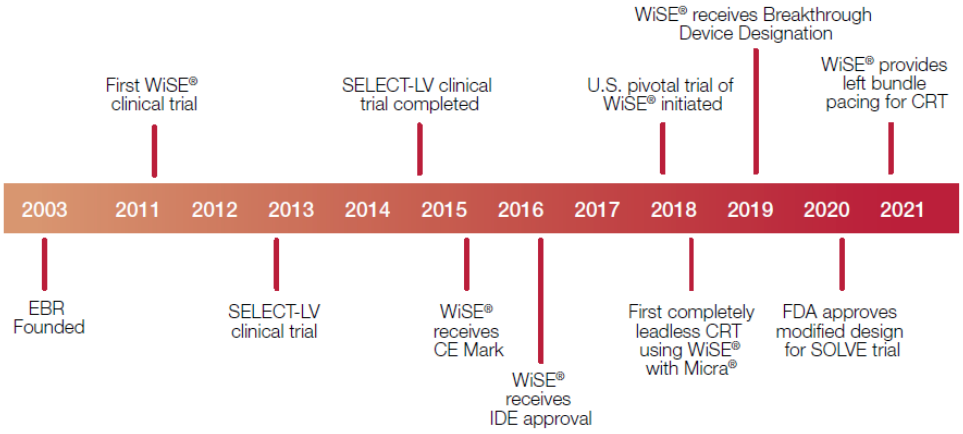


Source: Medtronic

Wireless ultrasound energy transmission is at the heart of it. The first iterations of WiSE utilised ultrasound energy to directly defibrillate the heart muscle but porcine studies revealed that such a direct approach caused tissue damage. In response, EBR pivoted from defibrillation to pacing and developed a receiving electrode to stimulate the cardiac tissue on the inner wall of the left ventricle.

The electrode was designed to harness wireless ultrasound energy, obviating the need for an internal battery source. This allowed a step-change in miniaturisation.

Figure 2. History of EBR highlighting key WiSE milestones



Source: EBR Systems

Funding rounds supported by same investor pool; currently own 40% stake. We note seven previous funding rounds to support EBR in development of their WiSE device, with the latest round in October 2019 raising US$30M. There have been several core investors in the past 3+ rounds who still maintain a significant portion of the EBR register including Brandon Capital Partners (19%), M.H. Carnegie (12%) and Split Rock Partners (9%). In addition, the CEO and Exec Chairman hold a combined ~5.6%.

2.2 Organisation

The business today. EBR Systems is located in Sunnyvale, California with approximately 75 staff comprised of the executive team, R&D expertise, regulatory, quality, clinical, manufacturing and finance/administrative functions of the company. EBR is primarily an R&D organisation today, engaged in equity-financed clinical trial development for WiSE. EBR does not generate material sales revenue.

EBR outsources the manufacturing of key components and sub-assemblies of their WiSE system to CDMOs however self-manage assembly of the final system/device and conduct quality and performance assessments of each system prior to sale/supply. We note a use of funds from the IPO as earmarked for scale up of manufacturing capacity ($6M) in preparation of US market entry following anticipated FDA approval.

WiSE has European CE mark and is in development to support FDA approval. The WiSE system received CE mark in 2015 allowing EBR to commercialise in the European market. EBR are currently still completing their pivotal SOLVE trial to support a potential FDA PMA approval in late ~2023e.

European business managed by EBR. EBR's European business functions are minimal at present and are focused on market preparation for full commercialisation of their WiSE CRT system. Since receiving CE Mark approval in 2015, EBR have established reimbursement for the WiSE system in several key European markets including the UK, as well as temporary reimbursement in France and Germany. To date EBR have not initiated sales and marketing efforts into Europe. This is expected to initiate coinciding with US launch (i.e. CY24e).

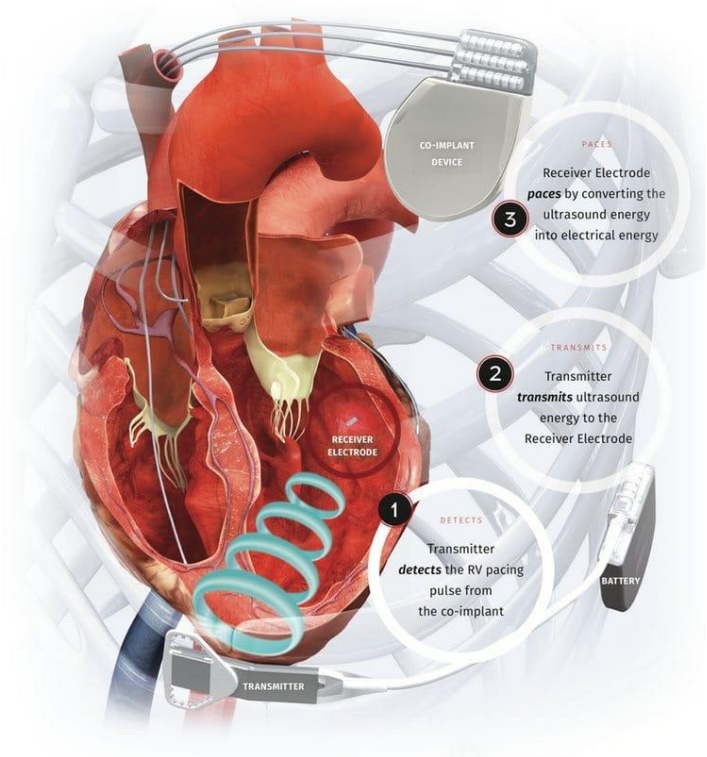
2.3 Technology summary

Wireless Stimulation Endocardially (WiSE) technology, in brief.

The WiSE system works to pace the two sides of the heart simultaneously, which is called cardiac resynchronisation therapy (CRT) or sometimes referred to as biventricular pacing. The WiSE system is differentiated from conventional CRT systems in that it dispenses with leads in stimulating the left ventricle (LV). Conventional CRT places a lead (wire) in the coronary sinus, a venous structure that wraps around the back of the heart, on the outer surface of the LV. As seen in **Figure 3**, the WiSE receiver electrode is a small device anchored in the inner wall of the left ventricle with no wires. It derives its pacing signals from a subcutaneous transmitter which works in unison with whichever co-implanted device is pacing the right side of the patient's heart (pacemakers, conventional CRT units, implantable defibrillator, leadless pacemakers). The electrode also derives its energy from the transmitter, in the form of wirelessly transmitted ultrasound.

Why leadless left ventricular pacing is important. Estimates vary but as high as 30% of heart failure patients who are eligible for CRT either do not receive it or experience sub-optimal results with conventional, lead-based CRT systems. Reasons are varied but include patients: a) whose vascular anatomy precludes the placement of leads; b) whose disease or comorbidities make lead implantation too risky to attempt; c) who are implanted successfully but develop complications requiring the device to be turned off or removed; or d) whose symptoms do not improve from receiving treatment. We assess a US$700M TAM in 2025 servicing these common clinical situations by 2025 (USA market).

Figure 3. Overview of the components of the WiSE CRT System

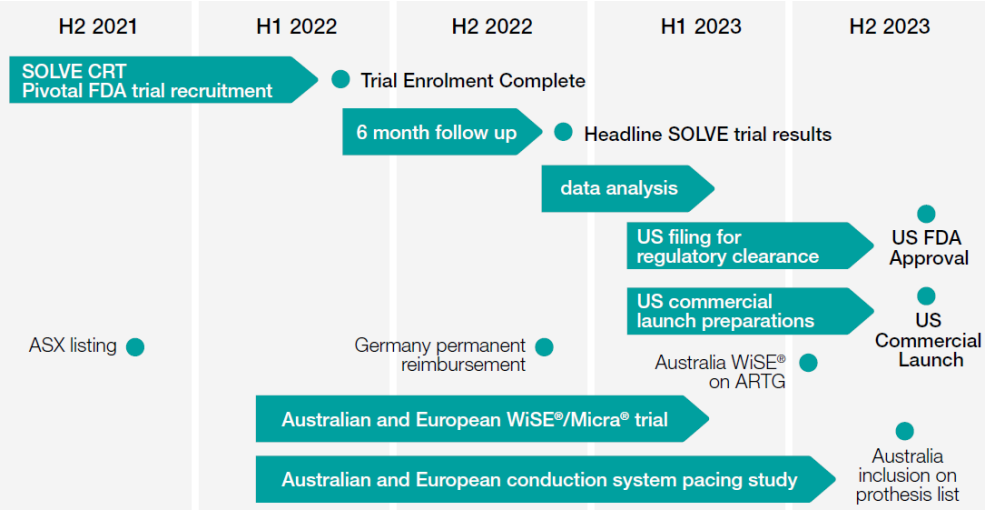


Source: EBR Systems.

2.4 Business direction and investment set-up

Regulatory approval and launch snapshot. As we initiate coverage on EBR the company is enrolling the third and final component of a large prospective clinical trial (SOLVE-CRT). Although approved in Europe, EBR has refrained from a large SG&A investment in that jurisdiction, waiting for a firmer evidence bases on which to launch fully. The SOLVE trial design allows a pre-specified interim analysis after 75 patients, the results of which should become available in late 2022. If certain safety and efficacy conditions are met the trial could be closed early at that point setting up an acceleration of the European business and potential FDA approval in 2H2023.

Figure 4. Anticipated regulatory and reimbursement milestones for WiSE CRT commercialisation



Source: EBR

In parallel, the leadless pacing market grows, setting up future opportunities for WiSE CRT. Competitors Abbott and Boston Scientific are following with their own leadless solutions. Although a new category (launched 2016) we estimate that the leadless pacemaker recipient population can reach 150,000 by 2025. Parts of this recipient population are likely to progress to heart failure or develop other forms of dyssynchrony at a relatively predictable rate, setting up an exclusive market for completely leadless CRT using WiSE. If approved, WiSE represents the only mechanism by which these recipients can be 'upgraded' to CRT without the introduction of lead wires.

Medtronic's leadless pacemaker business is run-rating US$440M in annual sales and growing at 15%.

3. Valuation

Initiating price target of $1.50 with upside to $3.40 on a 2-year view.

3.1 DCF valuation considerations

We approach the EBR Systems valuation using a discounted cash flow (DCF) model based on the revenue and earnings forecasts developed in Section 4. Briefly, we model the business using a direct sales model in the USA and international markets with FY32e net sales of US$437M. Table 1 shows our free cash flow estimates for FY22-32e which is our DCF valuation horizon. Note the protracted period of negative free cash flows as R&D and market development are undertaken. We forecast and value EBR in USD. We assess a risked DCF valuation of US$1.11 per share and covert that to AUD using a 12-month forward AUD/USD assumption of 0.74. Please refer to Section 4 for detailed information and assumptions behind our forecasts.

Table 1. Group level DCF valuation for EBR Systems

	FY22e	FY23e	FY24e	FY25e	FY26e	FY27e	FY28e	FY29e	FY30e	FY31e	FY32e
EBIT	(30.6)	(36.1)	(37.4)	(38.6)	(20.7)	(0.1)	41.4	67.6	95.2	117.0	132.1
EBITDA	(28.8)	(33.4)	(34.0)	(34.1)	(16.0)	4.6	47.1	75.2	105.0	128.7	145.2
Taxes	-	-	-	-	-	-	-	-	-	(29.2)	(33.0)
EBT (1 - t)	**(30.6)**	**(36.1)**	**(37.4)**	**(38.6)**	**(20.7)**	**(0.1)**	**41.4**	**67.6**	**95.2**	**87.8**	**99.1**
Add back D&A	1.8	2.7	3.4	4.5	4.7	4.7	5.7	7.7	9.9	11.7	13.1
Deduct capex	(3.4)	(3.5)	(3.7)	(4.2)	(5.0)	(5.0)	(5.3)	(5.8)	(6.7)	(7.8)	(9.1)
Change in w orking capital	(0.4)	(2.5)	(3.2)	(1.2)	(1.0)	(1.2)	(1.3)	(1.4)	(1.5)	(1.6)	(1.7)
FCFF	(32.6)	(39.4)	(40.9)	(39.5)	(22.0)	(1.6)	40.5	68.0	96.8	90.1	101.5
Cumulative discount rate	*110%*	*121%*	*133%*	*146%*	*161%*	*177%*	*195%*	*214%*	*236%*	*259%*	
Disc, risk-adj. FCFF	**(18.1)**	**(19.8)**	**(18.8)**	**(16.5)**	**(8.3)**	**(0.5)**	**12.7**	**19.4**	**25.1**	**21.2**	
Terminal value											**986.6**

Inputs	
Forecast period	FY22-32E
Risk-free rate	3.00%
Risk premium	6.00%
Valuation risks (blended)	60%
Beta	1.2
Cost of equity (discount rate)	10.0%
Tg	3.5%

Valuation	
PV of FCFF ($m) =	(3.7)
PV of Terminal Value ($m) =	380.6
Enterprise value Value ($m)=	376.9
- Net Debt (cash) , $m	(46.9)
Fully diluted shares	382.8

Equity Value (US$M) =	**424**
Price Target (US$/share)	**1.11**
Price target	**1.50**

Source: Wilsons' estimates

Important limitations. The WiSE CRT system is a genuinely new innovation in the global cardiac rhythm management medical device market. The only appropriate predicate to benchmark expectations against is Medtronic's Micra series of leadless pacemakers. Our WiSE CRT market penetration (and hence, sales) estimates are based on our best assessment of the proposed indications, the timing of major jurisdictional approvals, the number of eligible patients who stand to receive benefit and form the addressable market, as well as the propensity for heart failure physicians and electrophysiologists to adopt the WiSE approach. Furthermore, forecasting requires some intuition relating to future trends in clinical practice, including the evolution of alternative strategies. The second major limitation with DCF is that near term free cash flows are negative and all of the value resides in the terminal component, based on an FY32e earnings estimate.

Un-risked valuation $2.35 per CDI prior to indication expansion. We have risked our valuation using discrete probabilities of success for WiSE CRT's approval and earnings outlook as an asset. The former is essentially a 75% probability that the SOLVE-CRT trial produces evidence that supports FDA's approval of EBR's PMA filing. The latter reflects an 85% 'market access' probability that EBR's sales execution for WiSE CRT meets or exceed our forecasts. Setting both success probabilities to 100% provides an un-risked, fully diluted price target of US$1.62 (**A$2.35**) per CDI.

3.2 Option value of M&A

M&A the most likely way to crystallise value. The second way we look at valuing EBR is in the context of the company becoming a target for corporate activity and especially M&A. All global cardiovascular medical device franchises (Medtronic, Abbott, Boston Scientific, Edwards Lifesciences) have necessarily grown by M&A. In **Table 2** overleaf we provide a summary of cardiovascular M&A transactions over the last six years. Indeed, if WiSE CRT is successful in the clinic and with regulators, we see M&A as most likely mechanism by which shareholders win from their EBR holdings. All three of the major cardiac rhythm franchises (Medtronic, Abbott, Boston Scientific) stand to benefit from WiSE CRT in the same way. The most salient clinical indications stand separate from conventional CRT utilization, offering all players the means to bring non-responders, treatment failures and high-risk cases into the CRT market. There is a compelling commonality among potential acquires which could drive a strong premium in how EBR is valued in this context.

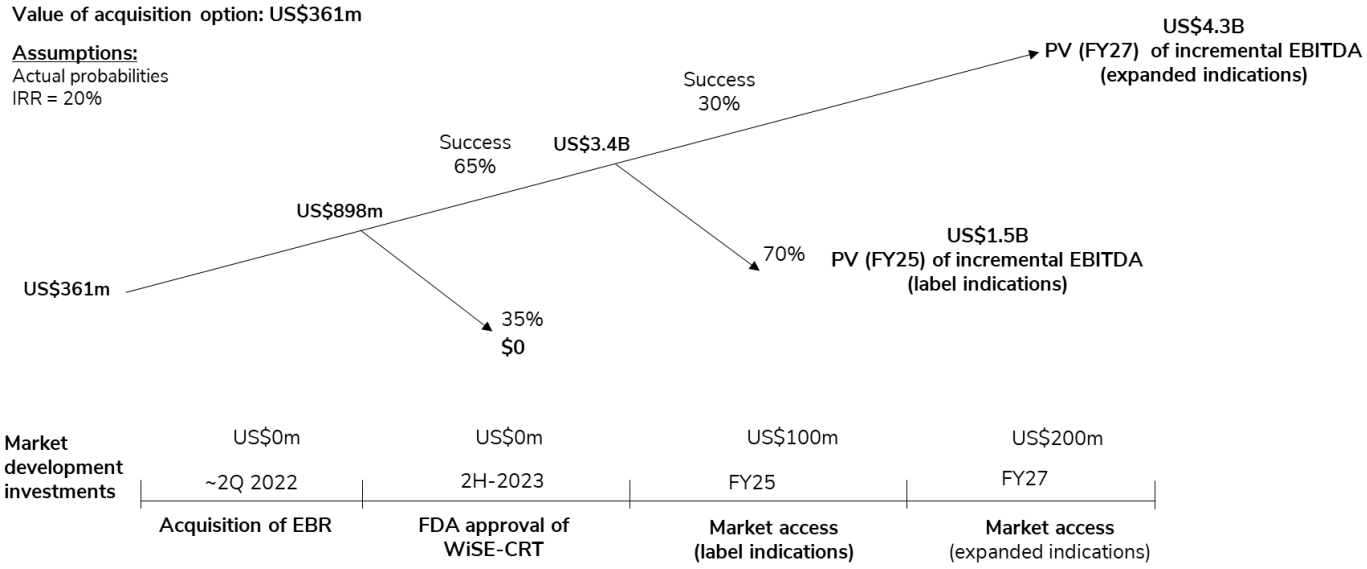
We have used a real-options technique to estimate potential acquisition valuations. Real-options is an attractive approach because it models the M&A transaction (from the acquirer's perspective) as a series of interacting, American-type options that lead to a future pay-off.

Conceptually:

- The acquisition price for EBR is modelled and priced as if it were an option premium paid by the acquirer.
- As the option holder, the acquirer then obtains subsequent, exclusive options to invest in WiSE CRT product and market development activities.
- The future pay-off driving the value of the options is the incremental EBITDA that WiSE CRT adds to the acquiror's rhythm management business.
- Option value is calculated using a binomial method that makes specific assumptions on project risks, timing and the desired rate of investment return.

The valuation approach is described further in **Figure 5**. Importantly, it represents a sample calculation from what is necessarily a complex, multivariate scenario. We provide a discussion of key drivers for the calculation over the page.

Figure 5. Real-option valuation (ROV) decision tree modelling prospective acquisition values for EBR.



Source: Wilsons

Assumptions

- **Upside values represent the future PVs of incremental WiSE CRT EBITDA with indication expansion optionality**. We model the upside (option pay-off) as a binomial outcome, considering two scenarios:
    a) Label indications only. Acquirer enters into the acquisition believing there is a 70% probability that WiSE will achieve our base case forecasts and only have access to labeled CRT indications: non-responders, lead failures, high-risk upgrades plus modest penetration into the leadless pacing recipient pool.
    b) Expanded indication upside. Acquirer enters into the EBR acquisition believing there is a 30% chance that they (as owners) can monetise WiSE in lower risk CRT upgrades, as an option for *de novo* CRT and in new situations enabled by conduction system pacing. Please see **Section 4.1.4** for a discussion of labelled and expanded TAMs.
        - Approximately 2.5x sales in expanded scenario. In **Section 4.1.4** we develop TAM estimates for the 2025 period based on immediately addressable markets (US$1.06B) and expanded settings (US$2.5B).

- **EBITDA assumptions**. For both base case and upside scenarios we model 72% gross margin and an incremental 15% EBITDA expense associated with WiSE CRT commercialisation. Note that potential acquirers under consideration (Medtronic *et al.)* have EBITDA margins of 30-33% in their core businesses. WiSE should be a straightforward addition to product portfolios, leveraging existing sales and marketing resources. The binomial pay-off drivers are therefore:
    a) Base case represents an FY25 PV of US$1.5B (label indications);
    b) Upside case represents an FY27 PV of US$4.3B (expanded indications).

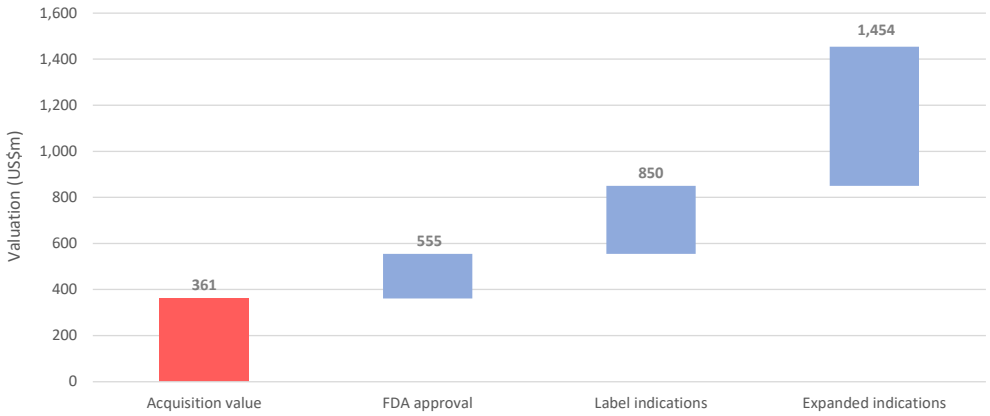
- **Stage-wise success probabilities and nested investment options.** We are modelling a transaction on the basis that at the time of the agreement, positive results from EBR's SOLVE-CRT trial are already known. From that point value develops through three further inflection points:
    a) FDA approval. We have assigned a 65% probability of success, assuming supportive data from the SOLVE-CRT pivotal trial. We assuming no incremental investment by the acquirer for this stage.
    b) Market access for label indications. We have assigned a 65% probability that WiSE meets or exceeds our base case assumptions. We assume a US$100M investment to the end of FY25 for market development.
    c) Market access for expanded indications. We have assigned a 30% probability that an expanded market for WiSE develops and assume a US$200M investment over 2 years to support this upside.
- **IRR of 20%.** In pricing the option to acquire EBR we have assumed an IRR of 20% (pre-tax) as the minimum required to justify the M&A investment decision. This accounts for time value of money over the 3.5 year investment horizon.

Outcomes and results from the analysis.

The valuation calculation works backwards from the upside values to arrive at an option value to acquire EBR. The methodology simultaneously adjusts for success probabilities and the time value of money. The result, in other words, is the amount that an acquirer could theoretically pay for EBR to make their desired return in view of the risks and investment amounts required.

- **EBR could be acquired for US$361M pre-FDA approval**. Extracting an A$481M EV takeover price in 2023 (SOLVE-CRT trial result catalyst) would imply A$1.69 per CDI or a 56% premium to the IPO price of A$1.08 per CDI.
- **EBR could be acquired for twice the valuation (US$898M) post-FDA approval**. Extracting an A$1,200M EV takeover price in 2024-5 would imply A$3.45 per CDI. This would represent a 2.2x outcome versus IPO pricing and a 47% premium to our un-risked DCF of A$2.35 per CDI.
- **M&A option valuation a valid way to look at EBR**. Clinical evidence and differentiation will be the key value drivers for the stock. Whilst DCF is perhaps more 'correct' as a technique it ignores the situational reality of how investors are more likely to make money from this clinical asset.
- **Acquirer upside is 40%-58% IRR, depending on market access outcomes.** Assuming an acquirer pays the option values we have calculated, the upside available to them is compelling. We assess +148% and +389% valuation uplift from the acquirer's perspective depending on market access outcomes. On an IRR basis and ignoring extraneous factors (transaction costs, etc.) we assess 53% IRR from the base case and 59% IRR for the longer dated upside scenario.

Figure 6. Valuation development from potential acquirer's perspective



Source: Wilsons

Table 2. Selected M&A transactions within cardiology (2015-2021)

Acquired target	Buyer	Date	Transaction value (A$)	Deal notes	Annual sales at acquisition
Oscor Inc (Private)	**Integer Holdings (NYSE:ITGR)**	28 Oct 2021	$291M	Oscor, Inc. designs, develops, manufactures, and markets implantable cardiac pacing leads, venous access systems, and diagnostic catheters in the United States and internationally.	US$76M
Baylis (Private)	**Boston Scientific** (NYSE:BSX)	6 Oct 2021	$2.4B	Structural heart product portfolio including radiofrequency (RF) catheter NRG and VersaCross Transseptal device as well as a family of guidewires, sheaths and dilators used to support left heart access. These platforms have advanced transseptal puncture to deliver therapies including atrial fibrillation ablation and WiSE CRT electrode placement.	US$200M annual sales.
Devoro Medical (Private)	**Boston Scientific** (NYSE:BSX)	21 Sep 2021	$465M	Devoro Medical developed the WOLF Thrombectomy Platform for clot retrieval from the arterial and venous systems.	Not reported
Farapulse Inc (Private)	**Boston Scientific** (NYSE:BSX)	24 Jun 2021	$510M	An electrophysiology device portfolio to include the FARAPULSE Pulsed Field Ablation (PFA) System – a non-thermal ablation system for the treatment of atrial fibrillation (AF) and other cardiac arrhythmias.	Not reported
PQBypass (Private)	**Endologix** (Private)	12 Apr 2021	$393M	Detour platform for percutaneous femoral-popliteal bypass device. Detour has FDA Breakthrough Device designation. The device comprises a TORUS stent graft and the PQ Crossing Device. The Detour System is currently being studied in a U.S. and European clinical trial, DETOUR2.	Pre-revenue
Carvida Medical (Private)	**Haemonetics** (NYSE: HAE)	20 Jan 2021	$807M	Vascular access devices.	US$60M
Millipede (Private)	**Boston Scientific** (NYSE:BSX)	27 Dec 2018	$640M	IRIS transcatheter ring system for annuloplasty.	Not disclosed.
St Jude Medical (NYSE: SJM)	**Abbott** (NYSE:ABT)	28 Apr 2016	$39.7B	St. Jude Medical develops, manufactures, and distributes cardiovascular medical devices for cardiac rhythm management, cardiovascular and atrial fibrillation therapy areas, and interventional pain therapy and neurostimulation devices for the management of chronic pain and movement disorder worldwide.	>US$4B
Valtech Cardio (Private)	HeartWare (NASDAQ:HTWR)	1 Sep 2015	$1.2B	Valtech Cardio Ltd. develops and manufactures cardiovascular devices for mitral regurgitation and tricuspid valve repair and replacement. The company specializes in transcatheter heart valve technologies for patients suffering from valvular insufficiency.	Pre-revenue
HeartWare (NASDAQ:HTWR)	**Medtronic** (NYSE:MDT)	8 Jun 2016	$1.7B	HeartWare International designs, develops, manufactures, and markets miniaturized implantable heart pumps or ventricular assist devices (VAD) for the treatment of advanced heart failure in the United States, Germany, and internationally.	Not disclosed
Medina Medical (Private)	**Medtronic** (NYSE:MDT)	31 Aug 2015	$308M	Medina Medical Inc. manufactures minimally-invasive devices for the treatment of brain aneurysms and stroke.	Pre-revenue
Lake Region Medical (Private)	**Integer Holdings** (NYSE:ITGR)	27 Aug 2015	$2.4B	Lake Region Medical manufactures and distributes medical devices for cardio, vascular, and advanced surgical markets. It offers electrophysiology ablation catheter devices; cardiac rhythm management systems, pacemakers, ICDs and CRT implantable pulse generators, neuro-modulation devices, neuro-stimulation leads, and implantable pulse generators.	Not disclosed
Twelve Inc (Private)	**Medtronic** (NYSE:MDT)	25 Aug 2015	$637M	Twelve owned medical devices for the treatment of chronic cardiovascular diseases such as valve replacement.	Not disclosed
Thoratec LLC	**St Jude Medical** (NYSE:ABT)	22 Jul 2015	$5.0B	Thoratec's primary product lines include ventricular assist devices, including HeartMate II, an implantable, electrically powered, continuous flow, left ventricular assist device (LVAD) consisting of a rotary blood pump designed to provide intermediate and long-term mechanical circulatory support (MCS); CentriMag an extracorporeal circulatory support device that provides hemodynamic stabilization in patients in need of cardiopulmonary support.	Not disclosed
CardiaAQ Valve (Private)	**Edwards** (NYSE:EW)	13 Jul 2019	$539M	CardiAQ develops and manufactures transcatheter mitral valve implantation (TMVI) systems. The company offers transcatheter system for mitral valve implantation to address mitral regurgitation. Its platform technology for TMVI systems includes a bioprosthetic transcatheter mitral valve, a delivery catheter, and a loading system.	Pre-revenue

Source: Capital IQ, Wilsons

3.3 Listed comparable companies

We have provided a selection of listed international medical device company valuation data for completeness only. EBR is too far from profitability for earnings capitalisation multiples. ASX-listed stocks typically trade at higher multiples – we observe a 50-75% premium on EV/EBITDA bases and >100% on EV/revenue. Midcap ASX-listed medical device can trade at grossly exaggerated (>20x) EV/revenue multiples when revenues are in an early growth phase and the business is perceived to be scalable with strong gross margins.

Table 3. Listed diagnostics developers as valuation benchmarks

Company Name	Ticker	Mkt cap ($M)	EV/EBITDA			EV/Revenue			Revenue growth		
			FY22e	FY23e	FY24e	FY22e	FY23e	FY24e	FY22e	FY23e	FY24e
International device											
Medtronic PLC	MDT	165,562	18.9x	17.3x	15.8x	5.8x	5.5x	5.2x	10.0%	5.6%	5.4%
Abbott Laboratories	ABT	224,219	18.1x	19.8x	17.9x	5.3x	5.6x	5.3x	24.6%	-5.2%	6.0%
Boston Scientific Corp	BSX	61,773	18.1x	16.6x	14.5x	5.2x	4.8x	4.4x	18.3%	8.7%	7.5%
Becton Dickinson and Co	BDX	70,439	12.9x	11.9x	10.6x	3.6x	3.4x	3.3x	-2.6%	5.4%	5.1%
Edwards Lifesciences Corp	EW	74,633	31.7x	28.2x	25.0x	10.6x	9.5x	8.6x	20.2%	11.4%	10.5%
Stryker Corp	SYK	103,909	21.1x	19.1x	17.6x	6.0x	5.6x	5.3x	18.4%	7.5%	6.9%
Zimmer Biomet Holdings Inc	ZBH	28,742	14.8x	13.5x	12.8x	5.0x	4.8x	4.6x	12.4%	4.2%	3.7%
NuVasive Inc	NUVA.OQ	2,946	11.3x	9.9x	9.0x	2.8x	2.6x	2.4x	12.2%	8.0%	6.4%
Mkt-cap weighted average			**19.4x**	**18.7x**	**16.9x**	**5.9x**	**5.7x**	**5.3x**			
ASX-listed device											
Resmed Inc	RMD.AX	51,775	27.7x	25.2x	23.0x	9.4x	8.9x	8.3x	23.0%	6.3%	7.3%
Cochlear Ltd	COH.AX	15,097	34.7x	30.5x	27.2x	9.5x	8.6x	7.8x	10.0%	10.7%	10.2%
Fisher & Paykel Healthcare Corporation Ltd	FPH.AX	17,485	31.7x	30.3x	26.7x	11.1x	10.7x	9.6x	-19.4%	4.0%	11.7%
Pro Medicus Ltd	PME.AX	6,175	90.3x	71.7x	57.5x	65.5x	53.5x	45.0x	33.8%	22.3%	18.9%
Nanosonics Ltd	NAN.AX	1,824	95.6x	62.2x	47.5x	13.3x	11.4x	10.0x	34.4%	16.7%	13.8%
Polynovo Ltd	PNV.AX	1,046		64.2x	27.8x	22.1x	13.9x	10.4x	59.7%	59.1%	33.9%
Aroa Biosurgery Ltd	ARX.AX	382				9.2x	7.6x	5.6x	63.1%	21.8%	36.5%
AVITA Medical Inc	AVH.AX	650				16.4x	12.5x	7.9x	34.7%	31.0%	58.6%
Medical Developments International Ltd	MVP.AX	359				12.6x	7.4x	5.3x	-1.1%	69.7%	39.3%
ImpediMed Ltd	IPD.AX	301			28.4x	8.3x	5.3x	2.9x	84.9%	56.7%	81.0%
Next Science Ltd	NXS.AX	248		24.3x	6.8x	11.0x	3.7x	2.3x	284.6%	202.0%	58.7%
Somnomed Ltd	SOM.AX	200		23.0x	17.5x	2.5x	2.2x	1.9x	13.6%	13.8%	15.7%
Mkt-cap weighted average			**33.9x**	**30.6x**	**26.7x**	**13.6x**	**12.1x**	**10.8x**			

Source: Refinitiv, Wilsons

FY24-26e valuation range of A$1.41 – A$4.74 at 15x EV/revenue. As an example, we apply 15x EV/revenue to out medium-term revenue forecasts and assess this to be a strong period for future valuation gains. Discounting these share price outcomes back to FY22 (10% WACC, unrisked basis) gives indicative price targets of **A$1.17 – A$3.24 per CDI**.

Table 4. Potential valuation outcomes in the medium term on the basis of 15x EV/revenue during WiSE CRT first 3 years of launch

	FY24e	FY25e	FY26e
Revenue	**19.6**	**40.3**	**84.7**
EV at 15x EV/revenue	**293.9**	**604.7**	**1,271.1**
Net cash	24.8	55.0	23.8
Equity value	318.8	659.7	1,294.9
Share count	300.4	347.1	364.1
Equity value per share (A$/CDI)	**1.41**	**2.53**	**4.74**
Discounted to FY22e (A$/CDI)	**1.17**	**1.90**	**3.24**

Source: Wilsons

3.4 Valuation sensitivities

Prior to evaluating sensitivities on the basis of obvious parameter variations (ASP, penetration profile assumptions) we summarise the variability around DCF having considered M&A optionality and what multiples could do in the medium term.

Figure 7. Valuation sensitivity by methodology



Source: Wilsons

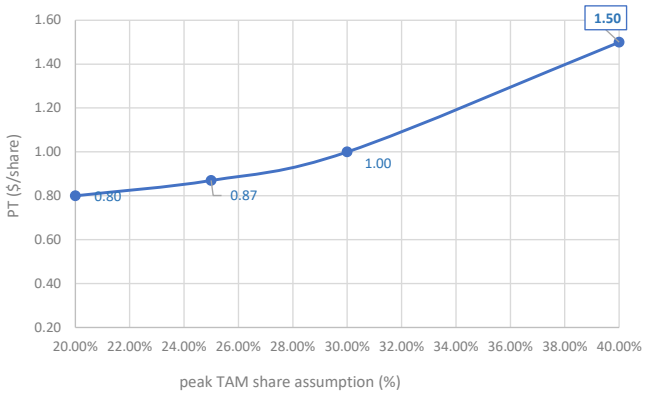
Commercial parameter variation. In **Table 5** below and **Figures 8-11** overleaf we provide the results of four scenario analyses. We varied our assumptions in relation to WiSE CRT ASP, peak TAM penetration and the pace of launch. We also assessed the impact of indication expansion which increases revenue potential by 150% but quadruple per CDI valuation.

Table 5. Drivers of valuation sensitivity

Sensitivity	Assumption *(deviation from base case)*	FY32 global revenue target	Δ PT	Revised PT range
TAM Share	Base case of 40% based on mature market TAM penetration achieved by CRT modality. Only downside scenarios examined to 20%. See **Figure 8**.	US$437M at base case falls to US$277M at 20% TAM share	Downside to -46%.	Down to $0.80
US WiSE CRT Pricing	Analysis examined the range US$10,000 to US$25,000 as a net ASP. PT a linear function of ASP with most of the impact at gross margin level assuming fixed unit manufacturing costs and constant SG&A restrictions. In our scenarios we assess an optimum price of ~US$370 per unit. At US$500 per prescription we assess lower net sales and valuation. See **Figure 9**.	US$509M to US$905M	-63% to +126%	$0.55 @US$10K $3.36 @US$25K
Penetration profile	Variance in the number of years to reach 50% of peak TAM penetration. Base case is 5 years. Explore sensitivities from 3 years to 9 years. See **Figure 10**.	US$285M to US$454M	-65% to +50%	$2.24 @ 3years $0.52 @ 9years
Indication expansion	Our base case assumes only labelled indications from SOLVE-CRT and leadless. We consider expansion of CRT indications, upgrades irrespective of risk category and new opportunities from conduction system pacing. See **Figure 11**.	US$437M to US$1,295M	Up to +300%	Up to $6.08

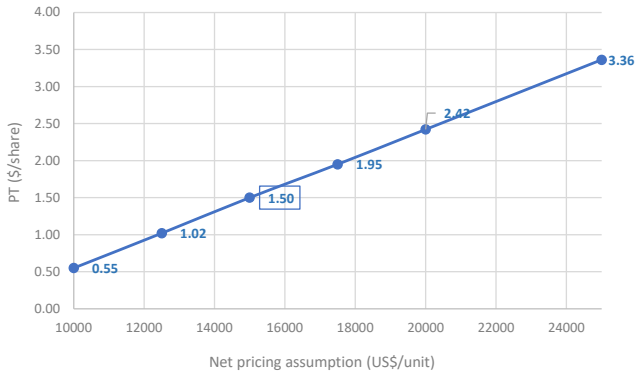
Source: Wilsons

Figure 8. PT sensitivity to variation peak TAM share in USA.



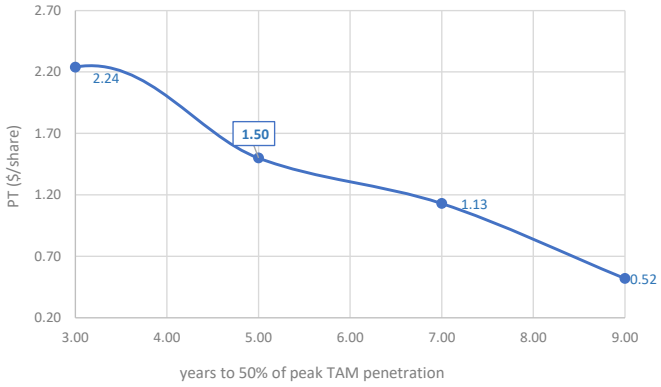
Source: Wilsons

Figure 9. PT sensitivity to US ASP assumptions.



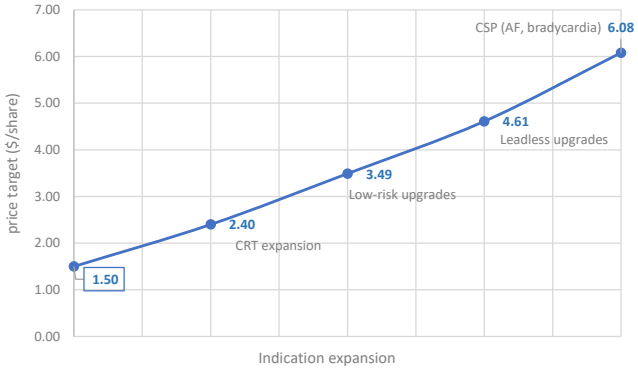
Source: Wilsons

Figure 10. PT sensitivity to speed of launch penetration profile (modelled as years to 50% peak TAM penetration.



Source: Wilsons

Figure 11. PT sensitivity indication expansion opportunities.



Source: Wilsons

3.5 Catalysts

In **Table 6** below we summarise key catalysts and relevant news flow expected for EBR and their relevant peer set over the next 2 years. Catalysts presented in bold represent key EBR-specific events. Shaded catalysts represent key events regarding relevant peers. Timing estimates provided.

Table 6. Near term catalysts and expected news flow relevant to EBR Systems

Date (CY)	Company	Event	Significance
1Q22	Various	1Q22 earnings for US peers (ABT, BSX, MDT)	Update on market growth, competitive positioning
1Q22	EBR	Appendix 4C	1Q22 quarterly progress update
April 3, 2022	Various	European Heart Rhythm Association (Copenhagen)	EHRA annual scientific meeting
April 29, 2022	Various	Heart Rhythm 2022 (San Francisco)	Key annual meeting
May 21, 2022	Various	Heart Failure 2022	Key annual meeting
1H22	**EBR**	**SOLVE-CRT enrolment completed (interim target)**	**First 75 patients in single-arm pivotal trial component for the purposes of interim analysis**
2Q22	Various	2Q22 earnings for US peers (ABT, BSX, MDT)	Update on market growth, competitive positioning
2Q22	EBR	Appendix 4C	2Q quarterly progress update
1H22	EBR	Commencement of AU/EU WiSE/Leadless pacemaker trial	Investigator-led, EBR-sponsored study combining WiSE CRT with leadless pacemakers (including upgrade and de novo implants).
1H22	EBR	Commencement of AU/EU conduction system pacing study	Prospective study using WiSE CRT for left bundle branch area pacing (LBBAP).
3Q22	Various	3Q22 earnings for US peers (ABT, BSX, MDT)	Update on market growth, competitive positioning
3Q22	EBR	Appendix 4C	3Q quarterly progress update
Aug 26-29	Various	ESC Congress (Barcelona)	Annual scientific meeting
2H22	**EBR**	**Interim SOLVE-CRT trial results**	**Potential to close SOLVE-CRT and commence PMA submission**
2H22	EBR	German reimbursement	EBR announces permanent reimbursement for WiSE in Germany
2H22	ABT	Aveir PMA approval	FDA approves Abbott's leadless pacemaker system.
4Q22	Various	4Q22 earnings for US peers (ABT, BSX, MDT)	Update on market growth, competitive positioning
4Q22	EBR	Appendix 4C	4Q quarterly progress update
Nov 5-7	Various	AHA Scientific Sessions	Annual meeting of the American Heart Association
1Q23	Various	1Q23 earnings for US peers (ABT, BSX, MDT)	Update on market growth, competitive positioning
1Q23	EBR	Appendix 4C	1Q quarterly progress update
1H23	EBR	Update on WiSE/Leadless pacemaker trial	Investigator-led, EBR-sponsored study combining WiSE CRT with leadless pacemakers (including upgrade and de novo implants).
2Q23	Various	2Q23 earnings for US peers (ABT, BSX, MDT)	Update on market growth, competitive positioning
2Q23	EBR	Appendix 4C	2Q quarterly progress update
2H23	**EBR**	**US FDA approval**	**Enables US launch of WiSE CRT**
2H23	EBR	WiSE CRT inclusion on Australian prosthesis list	Enables Australian reimbursement for WiSE CRT
3Q23	Various	3Q23 earnings for US peers (ABT, BSX, MDT)	Update on market growth, competitive positioning

Source: Wilsons, Company data

4. Financials and growth forecasts

4.1 Revenue

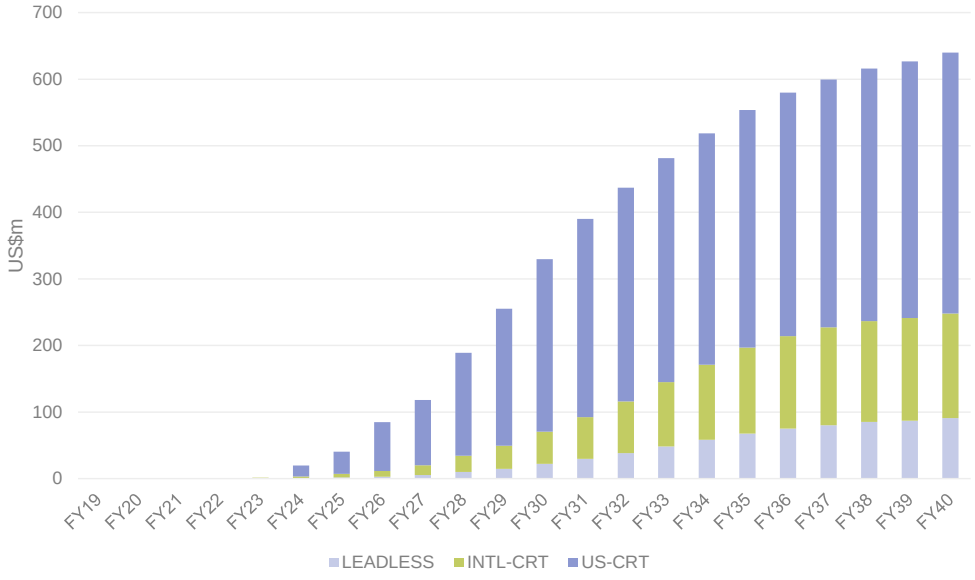
4.1.1 Model overview

EBR systems generates revenue through sales of WiSE CRT systems and ancillary catheter delivery systems. Our revenue forecasts are generated from a set of hierarchical market models that represent USA and International (INTL) as our two forecasting domains. Briefly on model structure:

- CRT model. A population-based model for the heart failure population with an indication for CRT. Target sub-populations include:
  - Non-responders to CRT;
  - CRT cases with coronary sinus (CS) lead failures (acute and chronic);
  - Upgrades from lead-based pacemakers and defibrillators needing biventricular pacing (CRT).
- Leadless pacing. The outlook for leadless single- and dual-chamber pacemakers. Target sub-indications include:
  - Upgrades to leadless CRT in patients who develop heart failure or dyssynchrony subsequent to leadless pacemaker implantation;
  - *De novo* leadless CRT in appropriate patient groups.

We therefore develop three revenue lines: US CRT, INTL CRT and Leadless pacing (global). We do not incorporate revenue from any other indications that might be enabled through conduction system pacing given that further clinical trials are required to validate WiSE in these settings. We estimate target net sales approaching US$650M without indication expansion into adjacent pacing strategies.

Figure 12. Sales revenue projections for WiSE CRT systems (FY19 – 40e)



Source: Wilsons

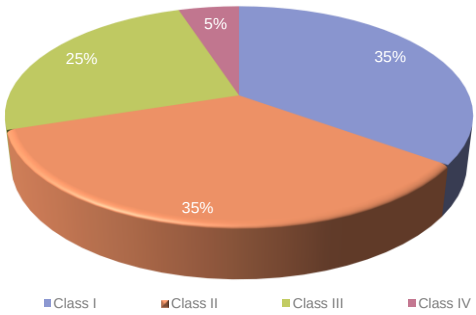
4.1.2 Modelling WiSE CRT device outlook in the USA HF population

Heart failure prevalence in the USA drives CRT market. The prevalence of heart failure (HF) continues to rise in the USA where we estimate a prevalent population of 6.4M people over the age of 20 in 2021. This patient population has grown consistently at ~2.5% CAGR since the early/mid-2000s when we covered the left ventricle assist device (LVAD) manufacturer HeartWare (HIN:AX)[4]. In this instance, we project continued growth in that market to reach 9M patients in the USA by 2040 (~1.8% CAGR). The fundamental drivers of HF (underlying cardiovascular disease, age, ethnicity, diabetes, obesity) remain unchecked. Epidemiologists continue to describe HF as an uncontrolled epidemic in the USA[5] with 5-year mortality of ~50%[6].

Discriminants of CRT candidacy. International CRT guidelines are reviewed in **Appendix A1**. There are differences between chronic heart failure with the following clinical features:

- In terms of symptoms: NHYA Class II, III or ambulatory Class IV despite optimal medical therapy are included as per **Figure 13**.
- Impaired cardiac function, adjudicated primarily on the basis of LV ejection fraction ≤ 35%. HF with reduced ejection fraction (HFrEF) constitute 50% of the entire HF population[7]. We assume that HFrEF prevalence is a function of NHYA status: Class II 50%; Class III 75%; Class IV 90%.
- Broadly inclusive assumption with respect to QRS duration (QRSd). Guideline support is strongest in patients with QRSd > 150 ms but CRT is 'considered' in certain cases > 130 ms. 25%-50% of all HF patients are believed to have QRSd > 120 ms[7] and we have assumed 35% for our base case model.
- We have not discriminated on the basis of left bundle branch block (LBBB) morphology because the guidelines are broadly inclusive on this factor, albeit with varied strength of recommendations.
- Atrial fibrillation (AF) occurs in 25% of patients undergoing CRT which results in a worse prognosis[8]. We model ~15% penetration within this off-label CRT population.
- In **Table 7** we have extracted a sample population breakdown for 2022 showing that approximately 15% of the total HF population fit within CRT guidelines.
- Assuming an average ASP of US$15,000 for CRT-P/D devices we estimate 159,000 system sales in 2022 or approximately 41% penetration of the addressable, untreated CRT-eligible population.

Figure 13. Breakdown of the US HF population by NYHA classification



Source: NHLBI

Table 7. USA CRT population delineation for 2022

2022 Estimates	
Heart failure population	6,587,366
NYHA Classes II-IV (65%)	4,281,788
HFrEF pts (LVEF ≤ 35%)	2,684,681
Sub-population with QRSd >130ms	939,638
- subtract AF patients	(234,910)
Guideline supported CRT population	**704,729**
- adjust for cumulative 5-yr mortality	(316,183)
Addressable, untreated CRT population	**388,546**
Estimated CRT system sales	**159,290**
De novo implants	103,539
Replacements and upgrades	55,752
Estimated CRT market penetration	**30%**

Source: Wilsons' estimates

[4] HeartWare was acquired by Medtronic in 2016 for US$1.1Bn. Medtronic discontinued the device in June 2021.
[5] Roger, V. (2021) *Epidemiology of heart failure: a contemporary perspective* Circ. Res 128: 1421 – 1434.
[6] Conrad, N. et al. (2019) *Temporal trends and patterns in mortality after incident heart failure: a longitudinal analysis of 86,000 individuals* JAMA Cardiol. 4: 1102 – 1111.
[7] Glikson, M. et al. (2021) *2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy* European Heart Journal 00: 1-94.
[8] Barold, S. S. et al. (2015) *Cardiac resynchronization in patients with atrial fibrillation* JAFIB 8

Modelling WiSE CRT candidacy. The CRT population drives our WiSE CRT market model, capturing the three target indications enabled by the SOLVE-CRT trial with off-label use in non-responders:

- **Acute lead failures** – patients who have a CRT indication but who are unable to have the lead implanted in their CS due to their anatomy or disease condition. We model this as 5% of treated CRT patients.
- **Chronic lead failures** – patients with an implanted CRT device that has had the CS lead switched off or the lead has become otherwise ineffective due to the lead failing or not functioning properly, or causing unwanted (phrenic nerve) stimulation. We model a 2% cumulative lead-failure rate, with the estimate for each year drawing surviving CRT recipients from the previous 8 years. We model an annual cohort mortality rate of 14% which approximates ~50% 5-year survival.

Table 8. Projected number of chronic lead failures presenting for WiSE CRT over 2022-2030e (USA m)

Potential Patient Population	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US CRT-treated patients	**159,290**	**166,738**	**168,164**	**171,632**	**176,134**	**181,143**	**185,109**	**189,027**	**193,139**
Surviving Patients Treated									
2012 Patients									
2013 Patients									
2014 Patients	37,734								
2015 Patients	50,305	43,262							
2016 Patients	60,268	51,831	44,574						
2017 Patients	58,609	50,404	43,347	37,279					
2018 Patients	72,280	62,161	53,458	45,974	39,538				
2019 Patients	88,354	75,985	65,347	56,198	48,331	41,564			
2020 Patients	107,558	92,500	79,550	68,413	58,835	50,598	43,514		
2021 Patients	130,908	112,581	96,819	83,265	71,608	61,583	52,961	45,546	
2022 Patients		136,989	117,811	101,317	87,133	74,934	64,444	55,421	47,662
2023 Patients			143,395	123,320	106,055	91,207	78,438	67,457	58,013
2024 Patients				144,621	124,374	106,962	91,987	79,109	68,034
2025 Patients					147,604	126,939	109,168	93,884	80,740
2026 Patients						151,476	130,269	112,031	96,347
2027 Patients							155,783	133,973	115,217
2028 Patients								159,194	136,907
2029 Patients									162,563
Cumulative surviving CRT recipients	606,016	625,712	644,302	660,387	683,477	705,263	726,564	746,617	765,483
Cumulative chronic lead failures	**12,120**	**12,514**	**12,886**	**13,208**	**13,670**	**14,105**	**14,531**	**14,932**	**15,310**

Source: Wilsons' estimates

- **High Risk Upgrade (HRU)** – patients with an existing pacemaker or ICD implant who subsequently develop heart failure requiring CRT but have a high risk of potential complications from upgrading to a conventional, lead based CRT system. We model this sub-population as 15% of treated CRT patients.
- **Non-responders -** approximately 30% of patients implanted with a CRT are classified as non-responders in that the device is operating normally but there is no symptomatic, electrical or structural improvement. Although this indication was not included in the final component of SOLVE-CRT we have included it in our market model. There is real-world data from Europe and Australia supporting it. In practice, there is potentially overlap with chronic lead failure.

Table 9. Sample USA WiSE CRT population delineation for 2025

2022 Estimates	
Acute lead failures	8,582
Chronic lead failures	13,208
High risk upgrades	17,163
Non-responders (off label)	8,582
Indicated WiSE CRT recipients	**47,534**
TAM at US$15,000 ASP	**US$713M**

Source: Wilsons

TAM estimate US$713M in 2025

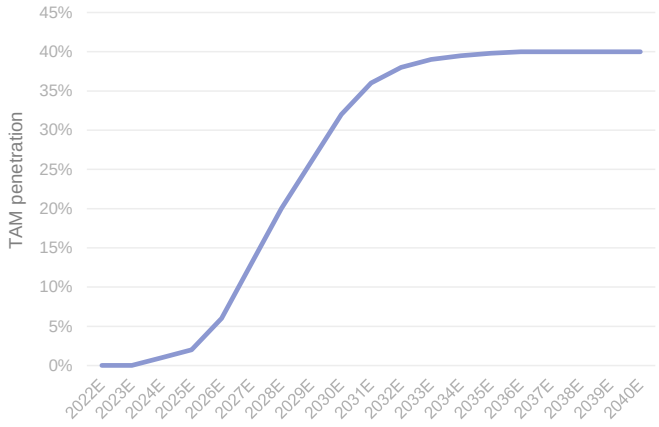
We assess an annual treatment market of over 47,500 WiSE CRT systems in the USA in 2025. If we assume ~US$15K as an ASP this implies a TAM of ~US$713M in 2022 growing to ~US$980M by 2040 (**Table 9**).

Pricing dynamics in the US market. As a CRT device, WiSE related procedures are likely to fall under existing reimbursement codes for conventional CRT in both inpatient and outpatient settings. These are bundled payments that cover all costs for the procedure including devices. If approved, hospitals implanting WiSE CRT are eligible for an additional New Technology Add-On Payment (NTAP) to cover the acquisition cost of the device. We estimate that as much as 65% of EBR's indicative ASP of US$35,000 could relate to the NTAP component. NTAP arrangements are typically in place for 2-3 years post approval and are designed to encourage the adoption of new technology. In the outpatient setting (ambulatory surgical centres) devices benefit from a Transitional Pass-Through (TPT) code which lasts for 3 years. During these NTAP/TPT periods CMS (and EBR) will collect information on usage and health economic outcomes to establish a regular market price for WiSE. We model an ASP of US$35K for the first 2.5 years of launch and then a flat US$15K from thereon.

Market access and share assumptions. EBR has provided a sketch of its post-approval roll-out plans for WiSE where 45 SOLVE clinical sites are likely to become first customers. EBR estimates these initial sites perform 10,000 conventional CRT implants a year (US$35-50M WiSE sales potential). Our model caps TAM penetration at 40% noting that that is the level conventional CRT has reached with three major device manufacturers driving it for nearly 20 years. The sigmoidal ramp we've used to model adoption is a guess (**Figure 14**). Our forecast is more conservative than EBR's aspirational target of >US$100M in FY25 (Wilsons: US$40M in FY25e).

We have included our long-run US sales projections over the page in **Table 10**.

Figure 14. Base case TAM penetration assumption



Source: Wilsons

Table 10. WiSE CRT USA model summary FY22-40e

Cardiac Resynchronization Therapy (CRT) for CHF and WiSE-CRT system sales estimates

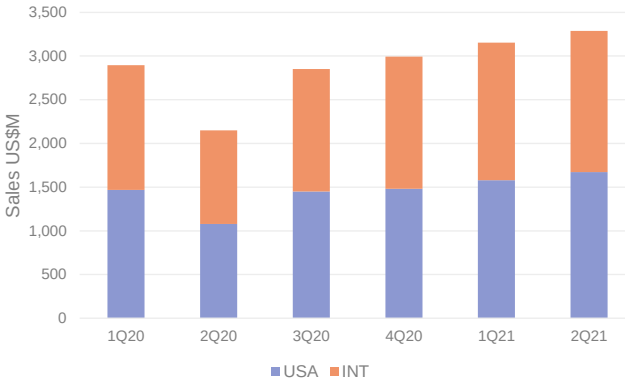
Potential Patient Population	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E
US Heart Failure Patient Population	6,587,366	6,735,582	6,885,449	7,034,863	7,183,651	7,331,634	7,478,633	7,624,466	7,768,950	7,911,899	8,053,126	8,192,445	8,329,669	8,464,609	8,597,080	8,726,896	8,853,873	8,977,827	9,098,579
NYHA Heart Failure Class II-IV	**4,281,788**	**4,378,128**	**4,475,542**	**4,572,661**	**4,669,373**	**4,765,562**	**4,861,111**	**4,955,903**	**5,049,817**	**5,142,734**	**5,234,532**	**5,325,089**	**5,414,285**	**5,501,996**	**5,588,102**	**5,672,483**	**5,755,017**	**5,835,587**	**5,914,076**
Percent with Ejection Fraction < 35%																			
No. of patients	2,684,681	2,745,087	2,806,165	2,867,058	2,927,697	2,988,007	3,047,917	3,107,351	3,166,236	3,224,494	3,282,052	3,338,831	3,394,756	3,449,751	3,503,740	3,556,647	3,608,396	3,658,913	3,708,126
Percent with QRS durations >130msec																			
No. of patients	939,638	960,780	982,158	1,003,470	1,024,694	1,045,803	1,066,771	1,087,573	1,108,182	1,128,573	1,148,718	1,168,591	1,188,165	1,207,413	1,226,309	1,244,826	1,262,939	1,280,620	1,297,844
Percent without Atrial Fibrillation																			
No. of patients	704,729	720,585	736,618	752,603	768,520	784,352	800,078	815,680	831,137	846,430	861,539	876,443	891,124	905,560	919,732	933,620	947,204	960,465	973,383
Guideline-supported Patient Population	704,729	720,585	736,618	752,603	768,520	784,352	800,078	815,680	831,137	846,430	861,539	876,443	891,124	905,560	919,732	933,620	947,204	960,465	973,383
Mortality-adjusted, Untreated Population	388,546	389,651	390,248	395,541	403,130	411,766	417,932	423,905	430,232	436,868	443,055	448,938	454,701	460,405	465,913	471,192	476,269	481,164	485,854
US CRT-treated patients	**159,290**	**166,738**	**168,164**	**171,632**	**176,134**	**181,143**	**185,109**	**189,027**	**193,139**	**197,428**	**201,553**	**205,577**	**209,580**	**213,590**	**217,543**	**221,421**	**225,236**	**228,994**	**232,684**
CRT-P	34,309	35,424	36,133	36,855	37,592	38,344	39,111	39,893	40,691	41,505	42,335	43,182	44,045	44,926	45,825	46,741	47,676	48,630	49,602
CRT-D	150,912	158,458	164,692	167,986	171,346	174,772	178,268	181,833	185,470	189,179	192,963	196,822	200,759	204,774	208,869	213,047	217,308	221,654	226,087
Penetration of Target U.S. Population	28.0%	29.1%	29.2%	29.4%	29.6%	29.8%	29.9%	30.1%	30.3%	30.5%	30.6%	30.8%	31.0%	31.2%	31.3%	31.5%	31.7%	31.9%	32.1%
WiSE-CRT candidates	**43,978**	**45,862**	**46,519**	**47,534**	**48,896**	**50,334**	**51,553**	**52,738**	**53,937**	**55,154**	**56,323**	**57,487**	**58,648**	**59,806**	**60,946**	**62,070**	**63,178**	**64,271**	**65,346**
Acute Lead Failures	7,965	8,337	8,408	8,582	8,807	9,057	9,255	9,451	9,657	9,871	10,078	10,279	10,479	10,679	10,877	11,071	11,262	11,450	11,634
Chronic Lead Failures	12,120	12,514	12,886	13,208	13,670	14,105	14,531	14,932	15,310	15,669	16,013	16,372	16,733	17,088	17,437	17,785	18,131	18,473	18,809
High Risk Upgrades	15,929	16,674	16,816	17,163	17,613	18,114	18,511	18,903	19,314	19,743	20,155	20,558	20,958	21,359	21,754	22,142	22,524	22,899	23,268
Non-responders	7,965	8,337	8,408	8,582	8,807	9,057	9,255	9,451	9,657	9,871	10,078	10,279	10,479	10,679	10,877	11,071	11,262	11,450	11,634
Market access/penetration profile	0%	0%	1%	2%	6%	13%	20%	26%	32%	36%	38%	39%	40%	40%	40%	40%	40%	40%	40%
WiSE-CRT System candidates[1]			465	951	2,934	6,543	10,311	13,712	17,260	19,855	21,403	22,420	23,166	23,803	24,378	24,828	25,271	25,709	24,831
Net ASP (US$ thousands)			35	35	25	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Net US sales (US$m)			**16.3**	**33.3**	**73.3**	**98.2**	**154.7**	**205.7**	**258.9**	**297.8**	**321.0**	**336.3**	**347.5**	**357.0**	**365.7**	**372.4**	**379.1**	**385.6**	**392.1**
- Sales growth				***104%***	***120%***	***34%***	***58%***	***33%***	***26%***	***15%***	***8%***	***5%***	***3%***	***3%***	***2%***	***2%***	***2%***	***2%***	***2%***

Source: Wilsons

4.1.3 Modelling WiSE CRT device outlook in the International (ex-US) HF population

Treatment of ex-USA markets. The three major players in global rhythm management report jurisdictional results showing that the US is broadly equal to the rest of world. **Figure 15** at right shows only sales for rhythm management, electrophysiology and heart failure (quarterly from 1Q20). We have taken a nominal approach to modelling ex-USA WiSE projections market basing our starting CRT patient population at ~60% of US levels. We chose this arbitrarily to reflect that EBR is likely to focus efforts on a small number of primary markets (e.g. Germany, UK) at least initially. All the assumptions and modelling approach we developed for the US market are retained in this model including choice of indications and exclusions. We are using the same 40% peak TAM penetration estimate but phasing it over a longer period time as the European market is usually more challenging to reach quickly, particularly for small companies. Note that our ASP assumption outside USA is equivalent to US$10,000 per system.

Figure 15. USA and International medical device sales by Boston Scientific, Abbott and Medtronic



Source: Boston Scientific, Abbott, Medtronic, Wilsons

INTL market TAM estimate of US$268M in 2025

We assess an annual treatment market of over 26,500 WiSE CRT systems in the INTL market by 2025. If we assume ~US$10K as an ASP this implies a TAM of ~US$268M in 2025 growing to ~US$392M by 2040 (see **Table 13** overleaf for a market model summary).

Table 11. INTL WiSE CRT population delineation for 2025

2025 Estimates	
Acute lead failures	5,149
Chronic lead failures	6,268
High risk upgrades	10,298
Non-responders (off label)	5,149
Indicated WiSE CRT recipients	**26,864**
TAM at US$10,000 ASP	**US$268M**

Source: Wilsons

4.1.4 Modelling the Leadless pacing aspect.

The third and final component of our revenue model is driven by the growth in the leadless pacing field (Medtronic's Micra; Abbott's Aveir; Boston Scientific's Empower). The model assumes sustained low double-digit growth in this category over the forecast period. Both modelled indications described below are driven by the cumulative number of leadless pacemaker recipients (adjusted for a 7% annual mortality assumption).

- **Leadless upgrades to CRT** – conventional RV pacing is associated with pacing-induced cardiomyopathy in 10-20% of patients after 2-4 years[9] (manifesting as HF or dyssynchrony both requiring CRT). We have assumed similar progression rates for leadless RV pacing and model that as a 2% cumulative function, drawing recipients from the previous 10 years. Note that WiSE CRT is the only option for upgrading these patients to an entirely leadless CRT modality.
- **De novo leadless CRT** – patients presenting with an indication for CRT and receiving a leadless pacemaker in their right ventricle and WiSE in their left ventricle at the outset. We model this as 7.5% of new leadless RV pacing sales.

Table 12. Sample Leadless WiSE CRT population delineation for 2025

2025 Estimates	
De novo leadless CRT	3,628
Leadless PM upgrades	3,046
Leadless CRT WiSE recipients	**6,675**
TAM at US$12,500 ASP	**US$83M**

Source: Wilsons

Leadless CRT market TAM estimate US$83M in 2025

We assess an annual treatment market of over 6,500 WiSE CRT systems for the leadless CRT market by 2025. If we assume ~US$12.5K as an ASP this implies a TAM of ~US$83M in 2025 growing to ~US$228M by 2040 (**Table 14**)

[9] Tayal, B. et al. (2019) *Incidence of heart failure after pacemaker implantation: a nationwide Danish Registry-based follow-up study* Eur. Heart J. 40: 3641 – 3648.

Table 13. WiSE CRT INTL model summary FY22-40e

Cardiac Resynchronization Therapy (CRT) for CHF and WiSE-CRT system sales estimates

Potential Patient Population	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E
US CRT-treated patients	**95,574**	**100,043**	**100,899**	**102,979**	**105,681**	**108,686**	**111,066**	**113,416**	**115,883**	**118,457**	**120,932**	**123,346**	**125,748**	**128,154**	**130,526**	**132,853**	**135,141**	**137,397**	**139,610**
CRT-P	28,672	30,013	30,270	30,894	31,704	32,606	33,320	34,025	34,765	35,537	36,280	37,004	37,724	38,446	39,158	39,856	40,542	41,219	41,883
CRT-D	66,902	70,030	70,629	72,086	73,976	76,080	77,746	79,391	81,118	82,920	84,652	86,342	88,023	89,708	91,368	92,997	94,599	96,178	97,727
WiSE-CRT Candidates	**22,879**	**24,705**	**25,720**	**26,864**	**28,096**	**29,326**	**30,383**	**31,383**	**32,362**	**33,092**	**33,794**	**34,492**	**35,189**	**35,884**	**36,568**	**37,242**	**37,907**	**38,563**	**39,208**
Acute Lead Failures	4,779	5,002	5,045	5,149	5,284	5,434	5,553	5,671	5,794	5,923	6,047	6,167	6,287	6,408	6,526	6,643	6,757	6,870	6,981
Chronic Lead Failures	3,764	4,696	5,540	6,268	6,960	7,588	8,169	8,700	9,186	9,401	9,608	9,823	10,040	10,253	10,462	10,671	10,879	11,084	11,285
High Risk Upgrades	9,557	10,004	10,090	10,298	10,568	10,869	11,107	11,342	11,588	11,846	12,093	12,335	12,575	12,815	13,053	13,285	13,514	13,740	13,961
Non-responders	4,779	5,002	5,045	5,149	5,284	5,434	5,553	5,671	5,794	5,923	6,047	6,167	6,287	6,408	6,526	6,643	6,757	6,870	6,981
Market penetration profile	0%	1%	1%	2%	3%	5%	8%	11%	15%	19%	23%	28%	32%	36%	38%	40%	40%	40%	40%
WiSE-CRT Systems	69	148	257	537	843	1,466	2,431	3,452	4,854	6,288	7,773	9,658	11,261	12,918	13,896	14,710	15,163	15,425	15,683
Net ASP	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Net INTL WiSE-CRT sales	**0.7**	**1.5**	**2.6**	**5.4**	**8.4**	**14.7**	**24.3**	**34.5**	**48.5**	**62.9**	**77.7**	**96.6**	**112.6**	**129.2**	**139.0**	**147.1**	**151.6**	**154.3**	**156.8**
- Sales growth		***116%***	***74%***	***109%***	***57%***	***74%***	***66%***	***42%***	***41%***	***30%***	***24%***	***24%***	***17%***	***15%***	***8%***	***6%***	***3%***	***2%***	***2%***

Source: Wilsons' estimates

Table 14. WiSE CRT global Leadless model summary FY22-40e

Potential Patient Population	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E
Leadless Pacemaker sales	**33,654**	**42,067**	**48,377**	**48,377**	**55,634**	**55,634**	**63,979**	**63,979**	**68,458**	**68,458**	**73,250**	**73,250**	**78,377**	**78,377**	**83,864**	**83,864**	**89,734**	**89,734**	**96,015**
Cumulative implanted population	54,544	82,024	115,405	152,318	186,647	225,321	260,111	298,392	332,504	365,277	391,255	416,842	436,850	457,387	476,486	496,084	514,310	532,964	550,312
WiSE-CRT candidates	**3,615**	**4,796**	**5,936**	**6,675**	**7,905**	**8,679**	**10,001**	**10,766**	**11,784**	**12,440**	**13,319**	**13,831**	**14,615**	**15,026**	**15,819**	**16,211**	**17,016**	**17,389**	**18,207**
WiSE de novo CRT	2,524	3,155	3,628	3,628	4,173	4,173	4,798	4,798	5,134	5,134	5,494	5,494	5,878	5,878	6,290	6,290	6,730	6,730	7,201
Leadless upgrades	1,091	1,640	2,308	3,046	3,733	4,506	5,202	5,968	6,650	7,306	7,825	8,337	8,737	9,148	9,530	9,922	10,286	10,659	11,006
Market penetration profile	0%	1%	1%	2%	3%	5%	8%	11%	15%	19%	23%	28%	32%	36%	38%	40%	40%	40%	40%
WiSE-CRT Systems	11	29	59	133	237	434	800	1,184	1,768	2,364	3,063	3,873	4,677	5,409	6,011	6,404	6,806	6,956	7,283
Net ASP	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500	12,500
Net Leadless sales	**0.1**	**0.4**	**0.7**	**1.7**	**3.0**	**5.4**	**10.0**	**14.8**	**22.1**	**29.5**	**38.3**	**48.4**	**58.5**	**67.6**	**75.1**	**80.0**	**85.1**	**86.9**	**91.0**
- Sales growth		***165%***	***106%***	***125%***	***78%***	***83%***	***84%***	***48%***	***49%***	***34%***	***30%***	***26%***	***21%***	***16%***	***11%***	***7%***	***6%***	***2%***	***5%***

Source: Wilsons' estimates

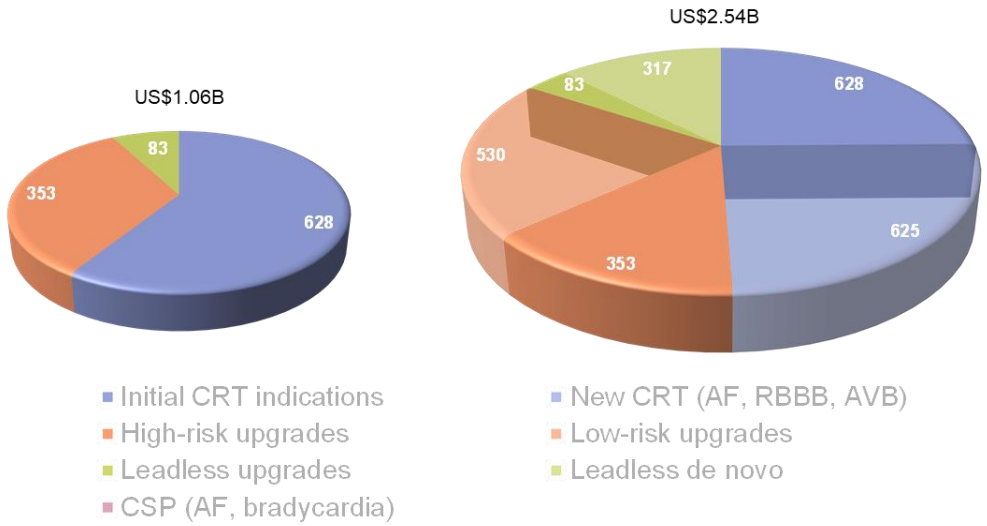
4.1.4 Potential revenue upside via indication expansion.

Non-high-risk upgrades from conventional CRT. On average, the number of upgrade CRT procedures is between 20% and 30% of all CRT implantations. Of those patients, approximately 60% have conventional RV pacemakers and 40% high-voltage ICDs[10]. The assumptions we made in modelling high risk upgrades imply 40% high-risk. Allowing all upgrades into the TAM assumption adds approximately US$530M in 2025 TAM.

First line, de *novo* implantation in preference to conventional CRT. We are modelling approximately 200,000 de *novo*, conventional CRT treatments (globally) in 2025 (excluding leadless de *novo*). We allow no attribution from this market. WiSE CRT will need to show enough benefit versus conventional CRT to offset the requirement for an additional component of implanted hardware (ultrasound transmitter and battery). Higher de *novo* penetration alongside leadless pacing is worth considering because it is already happening in a handful of European centres. We estimate an incident population for leadless pacemakers of 55,000 in 2025e of which 7.5% are receiving WiSE on account of access issues. We also adopted a very low rate of upgrades in our WiSE model. EBR estimates a potential 2023 WiSE/Micra TAM of ~US$400M.

Conduction system pacing (CSP). If WiSE CRT establishes itself in this setting there are at least three areas of indication and TAM expansion worth considering. The first we've touched on above in positioning versus conventional, 3-lead CRT systems on the basis of leadless physiological pacing. CSP also has potential to improve outcomes in specific situations including atrial fibrillation, right bundle branch block (RBBB) and atrioventricular block. Collectively we estimate these could represent up to 25% of conventional CRT procedures (50,000 devices in 2025). Finally, CSP has a potential role as an alternative to traditional RV pacing in de *novo* bradycardia. Again, the use case in bradycardia depends on CSP showing benefit over conventional pacemaker transvenous leads and leadless pacemakers. We have not allowed this into our scaled up, potential TAM estimate given the lack of evidentiary support at this stage.

Figure 16. We assess that indication expansion in CRT indications, leadless CRT and conduction system pacing has the potential to lift the WiSE CRT by 2.5X from base case assumptions (US$m).



Source: Wilsons

[10] Linde, C. M. et al. (2018) *Upgrades from a previous device compared to de novo cardiac resynchronization therapy in the European Society of Cardiology CRT Survey II.* Eur J Heart Fail;20:1457-1468.

4.2 Profitability

4.2.1 Gross profits

WiSE CRT units are manufactured at EBR's facility in Sunnyvale using components and sub-assemblies sourced from third parties. Our long-term gross margin assumption of 72% is based on analysis of larger peers Medtronic, Boston Scientific (both low-70%s) and Edwards Lifescience's TAVR business (mid-high 70%s).

Table 15 at right shows the jurisdictional differences in gross profitability recalling US and INTL ASPs of US$15K and US$10K, respectively. We allow for lower gross profitability in the early phases of commercialisation noting fixed manufacturing overheads at start-up. Higher margins become possible from FY25 following manufacturing scale-up to seek procurement efficiencies and optimise process yields.

Table 15. FY32E COGS analysis

2032Estimates	
WiSE unit sales	32,239
Net sales (US$m)	US$437m
Average ASP	**US$13,557**
Gross margin	72.0%
- US gross margin	74.7%
- INTL gross margin	62.0%
- Leadless CRT margin	69.6%

Source: Wilsons

4.2.2 Operating expenses

Research and Development. R&D expense was US$7.9M in FY20 and we expect to see similar expenditure in the current year as SOLVE-CRT moves back into full recruitment mode. We are forecasting an increase to US$12.2M in FY22e and US$14.1M in FY23e as EBR moves to support internal and investigator-initiated studies. On the R&D agenda:

- Completion of SOLVE-CRT;
- Longer term follow-up and real-world evidence development including post-marketing safety studies in Europe and Australia;
- Health economic analyses;
- Trial validation for completely leadless CRT in combination with leadless pacemakers;
- Feasibility and prospective safety and efficacy trials investigating leadless conduction system pacing in select indications (AF, AVB, bradycardia).

In the longer term we have assumed a routine R&D budget of 9% of net sales which includes the Clinical & Regulatory reporting line.

Sales and marketing. We forecast US$5.6M SG&A expense in FY21e largely for product field support and market development in Europe and Australia, supporting CE Mark. Our sales force assumptions have 5-6 immediate hires building out to a team of 12 over the next 12-18 months. As more organised forms of reimbursement become available we expect a national sales team of up to 60 individuals (2-3 years' time). We are forecasting SG&A to increase to US$8.4M next year and US$10.5M in FY23e as the company builds its US presence ahead of potential FDA approval and FY24e launch. Post launch, we forecast relatively aggressive expense growth as the sales and marketing organisation expands beyond the initial 45 clinical sites to engage another 200+ hospitals and ambulatory surgical centres. We note that FY23-25 are key commercialisation and market development years for EBR and hence SG&A expense is modelled at >60% of forecast net sales. On a longer run basis we model SG&A at 25% of net sales.

General and administrative. Our forecast allows for ~15% growth in non-market-facing, corporate headcount (incl. back office functions). Long run G&A assumption is 3% of net sales.

Interest. EBR has modest interest expense in relation to a loan from Silicon Valley Bank (SVB). SVB committed to three separate term loan advances to the Company, each in the amount of US$3 million for a total term loan commitment of US$9 million. The maturity date for the first two advances is 1 December 2022 and the maturity date for the third advance is 1 September 2023.

Depreciation and Amortisation. We forecast D&A expense as a stable 3-4% of revenues in line with historical expense averages.

EBITDA margin. We model EBITDA margin reaching ~33% in the outer years of our forecast. This is broadly in line with other international medical device companies we cover (e.g. COH, RMD, FPH).

Table 16. Income statement forecasts FY21-32e

Income statement	FY21	1H22	2H22	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30	FY31	FY32
Revenues														
WiSE-CRT CRT sales	-	0.5	0.7	1.2	1.7	18.9	38.6	81.8	112.8	179.0	240.2	307.4	360.7	398.8
WiSE-CRT Leadless sales	-	-	-	-	-	0.7	1.7	3.0	5.4	10.0	14.8	22.1	29.5	38.3
Total revenue	-	0.5	0.7	1.2	1.7	19.6	40.3	84.7	118.2	189.0	255.0	329.5	390.3	437.1
% growth vs pcp					*45%*	*1026%*	*106%*	*110%*	*40%*	*60%*	*35%*	*29%*	*18%*	*12%*
COGS	-	(0.2)	(0.3)	(0.5)	(0.7)	(7.5)	(14.7)	(30.1)	(37.8)	(56.7)	(75.2)	(93.8)	(109.3)	(122.4)
Gross Profit	0.0	0.3	0.4	0.7	1.1	12.1	25.6	54.7	80.5	132.3	179.8	235.7	281.0	314.7
gross margin %		*60%*	*60%*	*60%*	*62%*	*62%*	*64%*	*65%*	*68%*	*70%*	*71%*	*72%*	*72%*	*72%*
Other income	1.7	-	-	-	-	-	-	-	-	-	-	-	-	-
Operating Expenses														
Research and Development	(6.4)	(6.0)	(6.2)	(12.2)	(14.1)	(17.0)	(17.0)	(17.0)	(17.0)	(17.0)	(17.9)	(23.1)	(27.3)	(30.6)
% of revs		*1200%*	*879%*	*1013%*	*811%*	*87%*	*42%*	*20%*	*14%*	*9%*	*7%*	*7%*	*7%*	*7%*
Clinical and Regulatory	(5.4)	(3.0)	(3.5)	(6.5)	(7.2)	(7.9)	(8.2)	(8.5)	(8.8)	(9.2)	(9.6)	(10.0)	(10.3)	(10.8)
% of revs		*600%*	*500%*	*542%*	*411%*	*40%*	*20%*	*10%*	*7%*	*5%*	*4%*	*3%*	*3%*	*2%*
General and Administration	(2.3)	(1.5)	(2.0)	(3.5)	(4.2)	(5.2)	(6.5)	(8.2)	(9.0)	(9.9)	(10.9)	(12.0)	(13.1)	(14.5)
% of revs		*300%*	*286%*	*292%*	*240%*	*27%*	*16%*	*10%*	*8%*	*5%*	*4%*	*4%*	*3%*	*3%*
Sales and Marketing	(5.6)	(3.4)	(4.0)	(7.4)	(9.0)	(16.0)	(28.0)	(37.0)	(41.0)	(49.1)	(66.3)	(85.7)	(101.5)	(113.6)
% of revs		*680%*	*571%*	*617%*	*517%*	*82%*	*69%*	*44%*	*35%*	*26%*	*26%*	*26%*	*26%*	*26%*
EBITDA	(18.0)	(13.6)	(15.2)	(28.8)	(33.4)	(34.0)	(34.1)	(16.0)	4.6	47.1	75.2	105.0	128.7	145.2
EBITDA margin									*4%*	*25%*	*30%*	*32%*	*33%*	*33%*
D&A	(0.3)	(0.8)	(1.0)	(1.8)	(2.7)	(3.4)	(4.5)	(4.7)	(4.7)	(5.7)	(7.7)	(9.9)	(11.7)	(13.1)
EBIT	(18.3)	(14.4)	(16.2)	(30.6)	(36.1)	(37.4)	(38.6)	(20.7)	(0.1)	41.4	67.6	95.2	117.0	132.1
EBIT margin										*22%*	*27%*	*29%*	*30%*	*30%*
Net interest expense/finance costs	(0.4)	(0.1)	(0.1)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)
Profit (Loss) before tax (EBT)	(18.7)	(14.5)	(16.3)	(30.9)	(36.3)	(37.7)	(38.8)	(20.9)	(0.3)	41.2	67.4	94.9	116.8	131.9
Tax (expense)/credit	-	-	-	-	-	-	-	-	-	(10.3)	(16.8)	(23.7)	(29.2)	(33.0)
NPAT	(18.7)	(14.5)	(16.3)	(30.9)	(36.3)	(37.7)	(38.8)	(20.9)	(0.3)	30.9	50.5	71.2	87.6	98.9

Source: Wilsons

4.3 Balance sheet

EBR's summary balance sheet information is set out below in Table 17.

Table 17: Forecast balance sheet position as at end-FY21e

Balance sheet	FY21
Current Assets	
Cash	82.7
Receivables	0.1
Other (prepayments)	0.8
Inventories	-
Total current assets	**83.7**
Non-current assets	
Plant and equipment	1.3
Other non current assets	0.4
Total Non-current assets	**1.7**
Total Assets	**85.4**
Current liabilities	
Accounts payable	0.7
Accrued expenses	2.8
Borrowings	2.4
Other (deferred revs)	-
Total current liabilities	**5.9**
Non-current liabilities	
Borrowings	1.2
Other long term liabilities	0.4
Total non-current liabilities	**1.6**
Total liabilities	**7.4**
Net assets	**78.0**
Equity	
Contributed equity	306.2
Reserves	(3.1)
Accumulated Profit/losses	(225.2)
Total parent entity interest	**78.0**
Total equity	**78.0**

Source: EBR, Wilsons

Proceeds of IPO. Cash impact of the IPO was approximately US$72M (net) at A$1.08 per CDI. The transaction issued 101.8M new CDIs. Currently EBR reports a small amount of debt (SVB loan) which has US$2.4M repayable within 12 months. We forecast and end-FY21 net cash position of US$79.1 based on 2H21 net operating and investing outflows of US$10.3M.

Convertible notes. Prior to the IPO EBR issued convertible notes with an aggregate principal amount of US$17.4M. Immediately before the allotment of new CDIs the notes (plus interest) convert to 21.7M CDIs.

Other instruments. EBR's capital structure also comprises 28.6M options and 19.8M warrants with expiry dates ranging from 2022 to 2031. Our valuation is fully diluted for these securities.

4.4 Cash flows, capex, funding and shareholder returns

We summarise EBR's projected cash flow statements in Table 18.

Table 18. Summary cash flow details for EBR Systems FY22-29

Cash flows	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29
Cash flows from operating activities								
Receipts from customers	0.8	0.9	18.4	35.1	83.7	113.2	193.0	251.5
Payments to suppliers and employees	(30.0)	(36.8)	(55.6)	(79.6)	(108.8)	(114.6)	(144.0)	(185.9)
Cash from from operations	(29.2)	(35.9)	(37.2)	(44.5)	(25.1)	(1.4)	49.0	65.6
Interest expense	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)
Tax benefit (expense)	-	-	-	-	-	-	(12.3)	(20.2)
Total cash flow from operations	**(29.5)**	**(36.1)**	**(37.5)**	**(44.7)**	**(25.3)**	**(1.6)**	**36.4**	**45.1**
Cash flows from investing activities								
Total cash flows from investing activities	**(3.4)**	**(3.5)**	**(3.7)**	**(4.2)**	**(5.0)**	**(5.0)**	**(5.3)**	**(5.8)**
Cash flows from financing activities								
Debt issued	-	-	-	-	-	-	-	-
Proceeds from issue of shares (net)	-	65.0	-	85.0	-	-	-	-
Net interest income/(expense)	-	(3.9)	-	(5.1)	-	-	-	-
Payment of lease liabilities	**(2.9)**	**(1.6)**	**(0.8)**	**(0.8)**	**(0.8)**	**(0.8)**	**(0.8)**	**(0.8)**
Dividends paid	-	-	-	-	-	-	-	-
Net cash flow from financing activity	**(2.9)**	**59.5**	**(0.8)**	**79.1**	**(0.8)**	**(0.8)**	**(0.8)**	**(0.8)**
Changes in cash balance	(35.8)	19.9	(42.0)	30.1	(31.1)	(7.4)	30.3	38.5
Cash at Beginning of period	**67.2**	**28.2**	**47.8**	**81.5**	**37.7**	**24.6**	**33.5**	**64.5**
Fx adjustments	-	-	-	-	-	-	-	-
Cash at End of the half year	**46.9**	**66.8**	**24.8**	**55.0**	**23.8**	**16.4**	**46.7**	**85.2**

Source: Wilsons

Capex: EBR has flagged that US$6M of the IPO proceeds will be applied to scaling up manufacturing for FY23/24e US launch.

Funding requirements. On our base case projections we assess that EBR may have additional capital requirements over FY23-25 in order to adequately invest in the global launches of WiSE CRT. Note that our valuation and price target is pre-emptively diluted for these issuances. In the event that our forecasts are too conservative and EBR needs no further equity capital this would mean 20% upside to valuation and price target.

Appendices

A1. Cardiac resynchronisation therapy (CRT) market

A1.1 US$8.6B sales market in 2020 for cardiac rhythm management (CRM) devices

Cardiac rhythm management (CRM) is the largest individual medical device subcategory with 2020 sales > US$16B when one includes interventional electrophysiology and attendant imaging/diagnostic elements. The market segment for implantable rhythm management devices accounts for roughly half this market and includes three basic product categories:

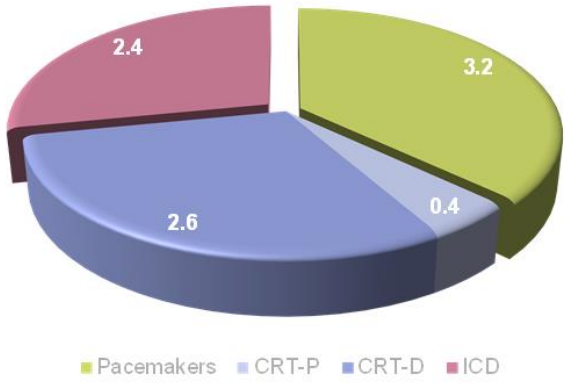
- Pacemakers – low voltage medical devices consisting of a pulse generator and transvenous leads implanted in the myocardium of the right atrium, ventricle or both. These devices sense the heart's underlying cardiac activity and provide therapeutic stimulation to maintain a normal rhythm. The most common indications for pacemaker implantation are sinus node dysfunction (bradycardia, sinoatrial block, bradycardia-tachycardia syndrome) and high-grade atrioventricular (AV) block. Pacemaker sales in 2020 were approximately US$3.2B.
- Implantable cardioverter defibrillators (ICDs) – high voltage medical devices that sense and treat potentially life-threatening arrhythmias. ICDs are indicated for prophylaxis against sudden cardiac death in patients who have survived cardiac arrest, with structural heart disease and or ischaemic cardiomyopathy. In 2020, ICD sales were approximately US$2.4B.
- Cardiac resynchronisation therapy (CRT) – medical devices that combine endocardial pacing in the right side of the heart and epicardial (conventionally) pacing for the left ventricle to ensure synchronous rhythm. CRT devices are available in two formats: a) CRT-P (pacemaker); and b) CRT-D (defibrillator). CRT is indicated for patients with left ventricle systolic dysfunction and dyssynchronous ventricular activation most commonly associated with heart failure with low ejection fraction (HFrEF). We assess US$3.0B in 2020 CRT sales of which 86% were CRT-D devices.

CRT market only 30% penetrated. We estimate 160,000 CRT unit sales in the US market in 2022 which is only 30% of the heart failure population that satisfy the labelled indication. The CRM market is dominated by three multinational medical device companies. The global market breaks down approximately 50:50 between USA and rest of world (INTL). Medtronic has the dominant share in both broad jurisdictions.

- USA market. We estimate US$4.3B sales in 2020 and 21% growth in the 1H of 2021 (COVID recoveries).
- International market. We estimate US$4.3B sales in 2020 and 32% growth over the 1H of 2021.

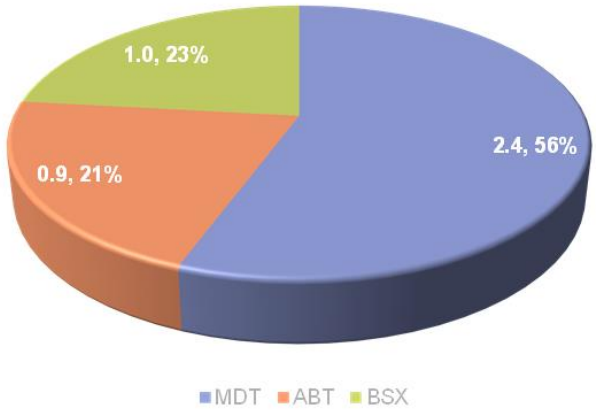
We are forecasting modest growth in the overall market with a gradual lift in penetration over time as WiSE provides solutions for non-responders and other under-treated cohorts. The emergence of leadless pacing solutions creates a captive market for leadless CRT as those patients develop a need for biventricular pacing.

Figure A1. We estimate US$3.0B CRT device sales in 2020 or 35% of the US$8.6B global CRM market.



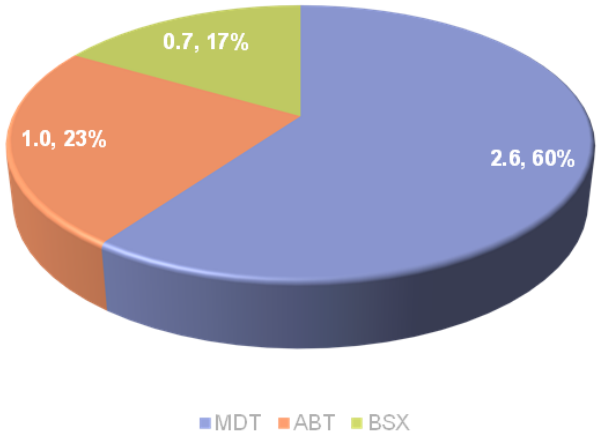
Source: MDT, ABT, BSX, Wilsons

Figure A2. USA CRM market sales (US$B) in 2020.



Source: MDT, ABT, BSX, Wilsons

Figure A3. International CRM market sales (US$B) in 2020



Source: MDT, ABT, BSX, Wilsons

A1.2 A review of clinical guidelines and indications for CRT

In this section we provide a review of relevant clinical guidelines in Europe, USA and ANZ. The European Society of Cardiology (ESC) has only recently updated its guidelines with an expanded view on CRT and new sections relevant to WiSE on conduction system pacing and leadless pacemakers. This review provided the basis for determining inclusion and exclusion criteria for our CRT and WiSE market models.

CRT guideline recommendations form a consensus for patients with LBBB and long QRS duration. There appears to be strong agreement between guidelines for HF patients with left bundle branch block (LBBB) and QRS duration >150ms. We note that LBBB occurs in ~30% of patients with HF (ranges of 10-40% reported in some studies)[11]. LBBB is also associated with low LVEF which is is a key patient inclusion criterion in its own right (uniform across guidelines in that patients with LVEF ≤ 35% should be indicated for CRT). The LBBB/QRSd determinant holds across different symptomatic classifications (NYHA classes II-IV, noting most guidelines pool Class III and ambulatory Class IV patients).

Guidelines controversial for some patient subgroups. We begin to see much more divergence between guidelines for other HF patient subgroups including NYHA Class I & IV patients, those with a moderate duration QRS interval (120-149ms) and those without LBBB. We have summarised the relevant guideline recommendation based on these factors (NYHA class, LBBB status & QRS duration) in **Table A1**.

Various guidelines cite meta-analyses of published CRT studies noting that patients with NYHA Class I and IV are underrepresented across CRT studies. One such meta-analysis showed that the most common HF candidate patients benefitting from CRT were those with LVEF ≤30% with a QRS interval duration >146ms[12]. No major guidelines include recommendations for NHYA Class I patients as indicated for CRT.

Table A1. Guideline comparison of where CRT is indicated within HF patient subgroups (QRS, LBBB, NYHA).

Guideline	LBBB						non-LBBB					
	QRS ≥150ms		QRS 130-149ms		QRS 120-129ms		QRS ≥150ms		QRS 130-149ms		QRS 120-129ms	
	NYHA III/IV	NYHA II	NYHA III/IV	NYHA II	NYHA III/IV	NYHA II	NYHA III/IV	NYHA II	NYHA III/IV	NYHA II	NYHA III/IV	NYHA II
ESC EHRA (2021)	Indicated	Indicated	Indicated	Indicated	Not indicated	Not indicated	Consider CRT	Consider CRT	Not indicated	Not indicated	Not indicated	Not indicated
ESC EHRA (2013)	Indicated	Indicated	Indicated	Indicated	Indicated	Indicated	Consider CRT	Consider CRT	May consider	May consider	May consider	May consider
ESC HFA (2016)	Indicated	Indicated	Indicated	Indicated	Not indicated	Not indicated	Consider CRT	Consider CRT	May consider	May consider	Not indicated	Not indicated
ACCF/AHA (2013)	Indicated	Indicated	Consider CRT	Consider CRT	Consider CRT	Consider CRT	Consider CRT	May consider	May consider	Not indicated	May consider	Not indicated
NHF/ACS ANZ (2018)	Indicated*		Indicated*		Not indicated*		Indicated*		Indicated*		Not indicated*	

**ANZ guidelines do not descriminate by NYHA class.*

Source: Wilsons, Almeida et al. (2017)[13].

Guidelines appear inconsistent; likely due to lack of Level 1 evidence to support recommendations. The challenge with development of evidence-based CRT guidelines is that there is a lack of Level 1 evidence. The changes between the European ESC guidelines between the 2013 iteration and the latest 2021 update highlight the disparity with regards to CRT clinical guideline recommendations and the level of evidence available to guide its use in different populations. In **Figure A4** we see four core recommendations flip between a strong level I recommendation to a level IIa consideration, or vice versa. This disparity suggests the clinical field are still very much trialling CRT in different populations and gaining the relevant evidence to guide clinical use on a dynamic basis. For this reason, the use of clinical guidelines to dictate CRT use cases for modelling purposes is likely flawed.

[11] Tabrizi F et al. (2007) *Influence of left bundle branch block on long-term mortality in a population with heart failure. European Heart Journal*. 28(20): 2449-2455.
[12] Cleland JG et al. (2013) An individual patient meta-analysis of five randomised trials assessing the effects of cardiac resynchronisation therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J*. 34(46): 3547-3556.
[13] Almeida ND et al. (2017) *Cardiac Resynchronisation Therapy in Heart Failure: Do Evidence-based Guidelines follow the Evidence?* Circulation: Cardiovascular Quality and Outcomes. 10 (12): e003554.

Figure A4. Changes in recommendation between ESC 2013 and 2021 clinical CRT guideline updates.

	2013	2021
	Class[a]	
Cardiac resynchronization therapy		
Patients who have received a conventional pacemaker or an ICD and who subsequently develop symptomatic HF with LVEF ≤35% despite OMT and who have a significant[b] proportion of RV pacing should be considered for upgrade to CRT.	I	IIa
CRT rather than RV pacing is recommended for patients with HFrEF (<40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB in order to reduce morbidity. This includes patients with AF.	IIa	I
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, a QRS duration of 130–149 ms, and LBBB QRS morphology despite OMT, to improve symptoms and reduce morbidity and mortality.	I	IIa
In patients with symptomatic AF and uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT is recommended in patients with HFrEF.	IIa	I

Source: Taken from ESC 2021 guidelines.

European guideline update suggests a trend of using CRT over RV pacing; evidence to support CRT upgrades lowered. Changes to the ESC 2021 guidelines (**Figure A4**) do suggest a strengthening in evidence for two patient subgroups; a) those with high-degree AVB, and b) those with AF that are candidates for AVJ ablation. CRT is now being recommended rather than RV pacing.

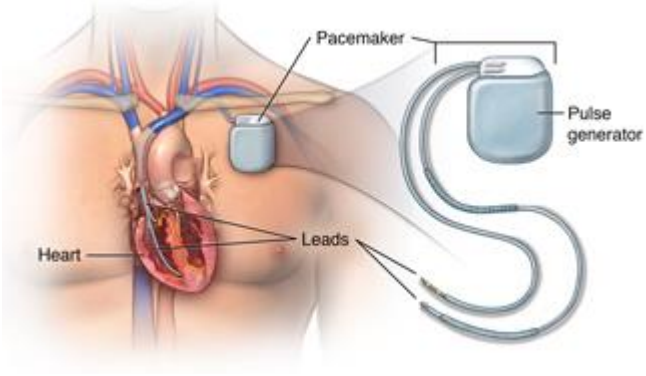
Further, evidence to support CRT upgrades was reduced from the prior iteration guidelines likely due to a range of observational studies showing non-significant benefits of CRT upgrade. We note the caveats to the evidence thus far with regard to CRT upgrades that does not evaluate comparable patient cohorts head to head (instead comparing *de novo* vs upgrade cohorts that differ in clinical severity and demographics).

A2. Leadless pacing

A2.1 What is leadless pacing and why it was developed

Pacemakers have been in routine clinical practice for nearly 60 years with essentially the same design format: a subcutaneously placed pulse generator connected to one or more leads. The leads are tunnelled via surrounding veins and placed inside or alongside the chambers of the heart. Once fixed into position they stimulate the tissue with either high or low voltage electrical energy. This restores the regularity of the heartbeat. In the most basic cases the right atrium only is paced. When the device needs to activate the right ventricle as well, that is known as dual-chamber pacing. The transvenous leads that carry the impulse are associated with both acute and chronic complications. Acute problems include not being able to place the leads safely or at all. More emergent clinical sequelae like deep vein thrombosis or pneumothorax are also reported. Chronic issues include venous obstruction, tricuspid valve insufficiency and infections[14].

Figure A5. Schematic for conventional lead-based pacemakers



Source: Heart of Melbourne Cardiology

Leadless pacing research began in the 1970s but only three systems have been studied in human trials. St Jude Medical's (now Abbott) Nanostim was the first device approved in the category (CE Mark in 2013) but was subsequently withdrawn on account of battery issues. At the time of writing Medtronic is the only manufacturer with a leadless pacemaker approval (Micra, FDA approved in 2016). Abbott has only just reported top line results for its Aveir implant and is expected to file a PMA in the coming months for late 2022 approval. Boston Scientific has a system (EMPOWER) in an ongoing pivotal trial with top line data expected in 2023.

A2.2 Clinical experience with leadless systems

Leadless pacing recommendations still new to guidelines

The explicit mention of leadless pacing only appears in the latest 2021 updated European ESC guidelines. Other international guidelines (>3 years old) are silent on the category. The first 6 years of leadless pacemaker availability have extended rather than cannibalised the market. Leadless pacemakers provide an alternative to transvenous pacemakers when no upper extremity venous access exists or when risk of device pocket infection is particularly high. At launch, Micra could only provide ventricular demand pacing (VVI) which restricted it to patients with atrial fibrillation or where only very infrequent pulses were needed (paroxysmal atrioventricular block or AVB). In 2020 Medtronic won an indication expansion to provide dual chamber pacing which increased the category's reach by ~40% treating AVB patients with more severe AV block.

FDA safety

FDA recently wrote to care providers about the risk of major complications if cardiac perforation occurs during leadless pacemaker implantation[15]. The Agency said that the overall risk of perforation is similar between leadless and conventional systems but Medtronic's Micra was associated with more severe complications than transvenous leads. FDA's letter referenced 90 deaths from >300 medical device reports (MDRs). FDA has not issued a Safety Communication in relation to Micra. The correspondence highlights the importance of training and following the device's instructions for use. With over 100,000 Micra implantations since 2016 the risk of complications and deaths remain well below 1% (considered an acceptable complication risk).

[14] Miller, M. A. *et al.* (2015) *Leadless cardiac pacemakers* JACC 66: 1179 – 1189.
[15] https://www.fda.gov/medical-devices/letters-health-care-providers/leadless-pacing-systems-risk-major-complications-related-cardiac-perforation-during-implantation?utm_medium=email&utm_source=govdelivery

Table A2. Leadless pacemakers in development

Abbott AVEIR	Boston Scientific EMPOWER	Medtronic MICRA
Trial ref: NCT04559945	Trial ref: NCT04798768	Trial ref: NCT02004873
Modes: single chamber only	Modes: in conjunction with standard implantable ICD	Modes: single or dual chamber







Source: Abbott, Boston Scientific, Medtronic, Wilsons

Evidence development remains in its formative years for leadless systems

There are no randomized controlled data available to compare clinical outcomes between leadless pacing and single-chamber transvenous pacing. Medtronic and associated investigators have set up patient registries to collect and track longitudinal outcomes, some of which have published results (Table A3). Encouragingly, the data so far from prospective registries show high success rates of implantation and supportive pacing characteristics.

Table A3. Summary of leadless pacemaker trials/registries

System	n	Follow-up	Success (%)	Safety and efficacy
St Jude Nanostim				
LEADLESS[16]	33	6 months	32/33 (97)	Complication rate = 3% (1 death after operation for tamponade). Adequate electrical performance at implant and follow-up.
LEADLESS II[17]	526	6 months	504/526 (96)	Complication rate = 6.5% (40 events in 34 patients). Adequate electrical performance at implant and follow-up.
LEADLESS Obv[18]	467	6 months	451/467 (97)	Complication rate = 10.6% (53 events in 50 of 467 patients). Adequate electrical performance at implant and follow-up.
Medtronic Micra				
Micra IDE study[19]	725	6 months	719/725 (99)	Complication rate = 3.4% (28 events in 25 of 725 patients). Adequate electrical performance at implant and follow-up.
Micra PAR[20]	795	30 days	792/795 (99)	Complication rate = 1.51% (13 events in 12 of 795 patients). Adequate electrical performance at implant and follow-up.
Micra Real-World[21]	1,817	6.8 ± 6.9 months	1,801/1,817 (99)	Complication rate = 2.7% (46 events in 40 of 1817 patients) Adequate electrical performance at implant and follow-up.
Abbott Aveir				
LEADLESS II Worldwide[22]	200	3.9 ± 1.9 months	196/200 (98)	Complication rate = 3% (3 tamponade events and 3 premature deployments). Adequate electrical performance at implant and follow-up.

Source: as referenced, Wilsons

[16] Knops, R.E. et al. (2015) *Chronic performance of a leadless cardiac pacemaker: 1-year follow-up of the LEADLESS trial.* J Am Coll Cardiol 65:1497-1504.
[17] Reddy, V.Y. et al. (2015) *Percutaneous implantation of an entirely intracardiac leadless pacemaker.* NEJM 373:1125-1135.
[18] Sperzel, J. et al. (2018) *Primary safety results from the LEADLESS Observational Study.* Europace 20:1491-1497.
[19] Reynolds D et al. 2016. A leadless Intracardiac Transcatheter Pacing System. *NEJM.* 374: 533-541.
[20] Roberts, P. R. et al. (2017) *A leadless pacemaker in the real-world setting: the Micra Transcatheter Pacing System Post-Approval Registry.* Heart Rhythm 14:1375-1379.
[21] El-Chami, M.F. et al. (2018) Updated performance of the Micra transcatheter pacemaker in the real-world setting: a comparison to the investigational study and a transvenous historical control. Heart Rhythm 15:1800-1807.
[22] Reddy, V. Y. et al. (2021) *Primary results on safety and efficacy from the LEADLESS II-Phase 2 worldwide clinical trial* JACEP 1602.

A2.3 Medtronic's Micra – evidence summary in more detail

A significant portion of WiSE CRT's future depends on the success of the leadless pacemaker category. A detailed review of safety, efficacy and indications is warranted, if only to interrogate Medtronic's aspirations of it building to a US$2Bn sales category. The most recent update on real-world evidence for their leadless pacemaker (Micra) was published in Nov 2021.

Micra Coverage and Evidence Development (CED) study. A prospective, continuously enrolling, observational study comparing outcomes after a 2 year follow up period[23]. Study focused on US Medicare beneficiaries receiving either Micra leadless PM (n=6,219) or transvenous PMs (n=10,212).

Key takeaways:

- No change in all-cause mortality (2 year follow up) between transvenous and leadless PMs (HR 0.97, p=0.37).
- Leadless Micra patients had significantly fewer (38% less) reinterventions vs traditional pacemakers (HR 0.62, p=0.003).
- Leadless Micra patients had significantly fewer (31% less) chronic complications vs traditional pacemakers (HR 0.69, p<0.0001).
- Patients receiving leadless Micra PM were more ill and still had better outcomes; 12% with End Stage Renal Disease vs 2% in transvenous PM cohort, plus a higher Charlson Comorbidity Index (CCI) score (mean 5.1 vs 4.6).

Micra IDE study. A prospective, non-randomised, single arm, multisite, global study to evaluate the safety and efficacy of the Micra leadless pacemaker device. This study supported Medtronic's US IDE approval. The study enrolled 744 patients across 19 countries, of which 725 completed Micra implantation. These patients were divided into those with persistent/permanent tachyarrhythmia (64%), sinus-node dysfunction (17.5%), AVB (14.8%) or other (3.7%).

Only 6.2% of patients were indicated for leadless pacing due to them not being candidates for transvenous PM implant (due to compromised venous access, infection history, thrombosis, preservation of veins for haemodialysis or need for indwelling venous catheter). 99.2% (719/725) of implantations were successful.

In a post-hoc analysis the results were compared to a control cohort of transvenous PMs (n=2667) to evaluate complication rates, hospitalisations and system revisions. The study cohort were older with more comorbidities than the post-hoc comparator control cohorts.

Key takeaways:

- Prespecified safety performance goal for study was 83% freedom from system or procedure related complications at 6 months post-implantation. Study achieved 96% (p<0.001).
- Post-hoc analysis with a control cohort showed lower major complication rates with Micra (4% vs 7.4%, HR 0.49, p=0.001), fewer hospitalisations (2.3% vs 3.9%) and fewer system revisions due to complications (0.4% vs 3.5%).
- Post-hoc analysis showed no significant differences between Micra and transvenous controls with respect to pacing issues, cardiac injury events or access-site events.
- Prespecified efficacy performance goal for the study was 80% for capture of an adequate 6-month pacing capture threshold. Only 297 patients were included in the primary efficacy analysis with 6-month threshold data. 292/297 (98.3%) achieved adequate 6-month pacing threshold (p<0.001).

[23] El-Chami MF et *al*. 2021. Leadless vs. transvenous single-chamber ventricular pacing in the Micra CED study: 2-year follow-up. *European Heart Journal*. 00: 1-9.

Long term follow-up (12-months) from Micra IDE study. A pre-specified long-term safety and efficacy follow up was conducted as part of the Micra IDE study, which was published in 2017[24]. The focus of this follow up study was the electrical performance of the Micra device at 24 months post-implantation (battery life) plus the long-term safety with regards to freedom from complications.

Key takeaways:

- Prespecified safety performance goal for study was 82% freedom from system or procedure related complications at 12 months post-implantation. Study maintained 96% ($p<0.0001$).
- Post hoc analysis comparisons showed the risk of major complications was 48% lower in Micra vs transvenous PM cohort control at 12 months post implantation (4.0% vs 7.6%; HR 0.52, $p=0.001$). Based on data from 726 Micra patients.
- Reduction in major complications driven by 47% relative risk reduction in hospitalisations ($p<0.05$) and 82% relative risk reduction in system revisions ($p\leq0.001$).
- Electrical performance of Micra device at 24 months post implantation was good; estimated battery longevity of 12.1 years (89% of patients having projected longevity of > 10 years) from 12 months of use data.
- Loss of device function reported in 0.3% of cases (i.e. ~2 cases of 726).
- 2 patients in study had major complications related to pacemaker syndrome; both were upgraded (1 to dual chamber pacing, 1 to CRT).

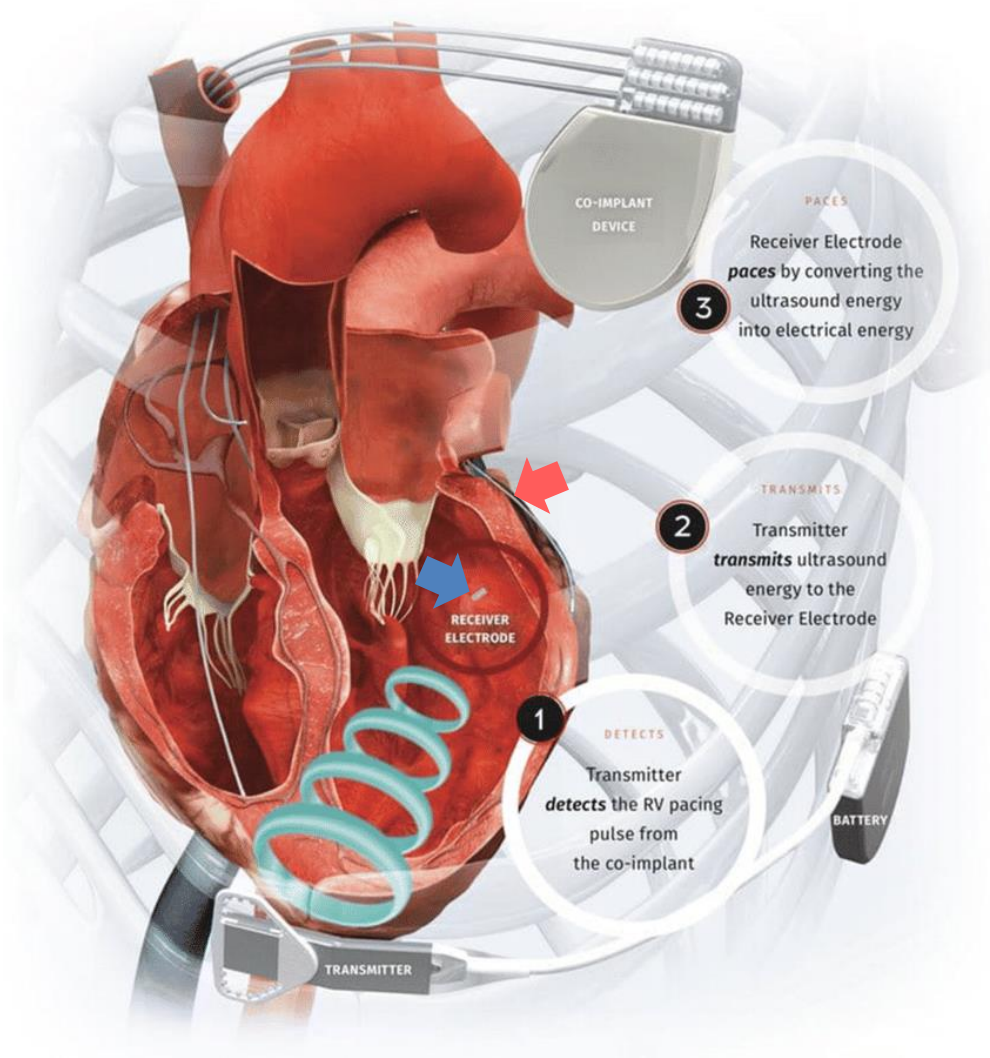
[24] Duray G et *al.* 2017. Long-term performance of a transcatheter pacing system: 12-month results from the Micra Transcatheter Pacing Study. *Heart Rhythm*. 14: 702-709.

A3. The WiSE CRT System

A3.1 Overview

WiSE CRT is the first and only medical device system to pace the left ventricle from the inside without using external leads fed by a pulse generator. **Figure A6** below shows the WiSE CRT system in contrast to a conventional 3-lead CRT system which paces the left ventricle from an external (epicardial) position via the coronary sinus. In the first instance, WiSE's small receiver electrode replaces that function but paces from the inside wall (endocardium) of the left ventricle. The system is composed of an ultrasound pulse generator, a battery, a receiver electrode (and delivery system for surgical deployment) and a programmer unit. In its current configuration WiSE must be used in concert with a co-implanted cardiac rhythm management device on the right side of the heart. This co-implanted device can be any single- or dual-chamber pacemaker, ICD or conventional CRT system (manufacturer-agnostic).

Figure A6. WiSE CRT deploys a receiver electrode (blue arrow) in the LV endocardium to provide CRT for patients who cannot be implanted with a conventional epicardial lead via the coronary sinus (red arrow).



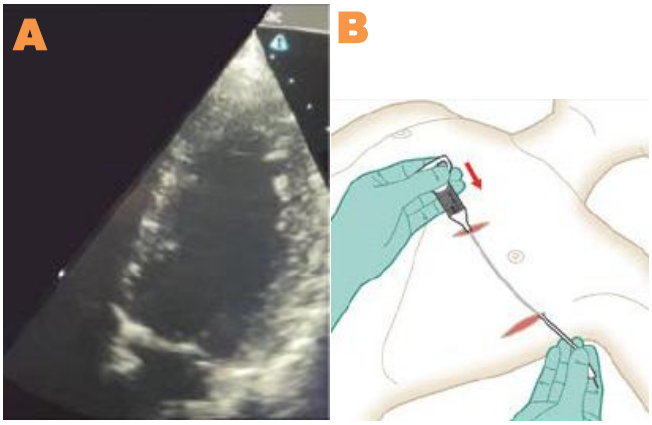
Source: EBR, Wilsons

Wireless ultrasound transmission. The WiSE transmitter is where the crux of EBR's intellectual property position resides, performing three functions:

- It detects pacing signals from the right ventricle via the co-implanted device;
- Converts that signal into an ultrasound pulse;
- Transmits that ultrasound pulse wirelessly to the receiver electrode implant.

Note that the transmitter/battery units are always implanted first after being screened using an external ultrasound examination to ensure an acoustic window (**Figure A7**). The transmitter and the battery that powers it are both implanted subcutaneously and joined by a tunnelled cable. Experience with the system has found that placing the transmitter between the 4th to 7th intercostal space (between the ribs) ensures that there is an 'acoustic window' with line of sight to the transmitter. Approximately 5-8% of potential candidates are screened out on this basis as encroaching lung, bone or other structures could impede the wireless ultrasound transmission.

Figure A7. (A) Ultrasound image showing a whole left ventricle from an intercostal space, confirming an acoustic window. (B) Approximate 'pocket incisions' allowing the subcutaneous placement of WiSE transmitter and battery.



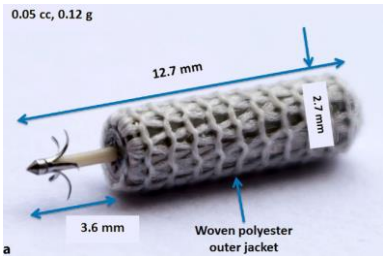
Source: Sidhu (2021)[25]

Electrode placement and function. The WiSE electrode component is shown at right in detail (**Figure A8**). The body of the device is actually a single chamber pacemaker that is hermetically sealed in a capsule and housed within a polyester outer jacket. The pacemaker contains no battery of its own but transduces electrical pulses to the heart tissue via a piezoelectric element which in turn is energized by the ultrasound signal from the transmitter. Each pulse from the transmitter has two components: a) a low energy pulse capable of locating the electrode but not enough to pace the ventricle; and b) a stronger, directed pulse (2-5 ms later) which captures the left ventricle and stimulates biventricular pacing.

The outer coat has a woven structure to encourage the nucleation of cell and tissue growth on the surface (**Figure A9**). The concept behind this design element was to minimise the risk of thrombosis by encapsulating the electrode within the endocardium. At the distal end of the electrode is a 3.6 mm barbed, insulated, tine structure which facilitates anchoring in the endocardium. It also provides the contact point through which electrical stimulation of the tissue is delivered.

Theoretically the electrode can pace from any position inside the LV but obviously the angle and distance from the transmitter are constraints. The greater the separation between the two components, the more energy is required to 'capture' the electrode and this will ultimately reduce battery life. A number of modalities are available to optimise placement prior to and during the implantation procedure. Electrophysiologists use mapping catheters and imaging techniques (trans-oesophageal ultrasound, fluoroscopy) to find conductive sites on the endocardium that are free from scar (prior infarction).

Figure A8. WiSE electrode detail



Source: EBR

Figure A9. Endothelialized WiSE electrode



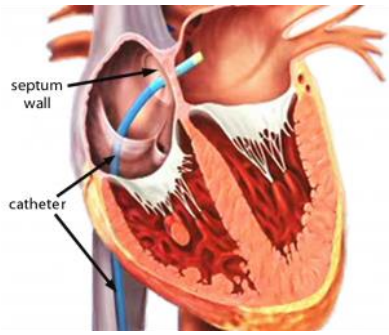
Source: Butter(2018)[26]

[25] Sidhu, B. S. et al. (2021) *Leadless left ventricular pacing and left bundle branch area pacing for cardiac resynchronization therapy* Arrhythmia & Electrophysiology Review 10(1):45–50.
[26] Butter, C. et al. (2018) *WiSE CRT alternative to conventional pacing (German)* Herzschr. Elektrophys. 29: 340 – 348.

Delivery systems. Early experimentation with WiSE favoured access via the femoral artery because it offered a more direct route to the left ventricle via the aorta. Delivery catheters are introduced into the femoral artery and guided up in the opposite direction of blood flow (retrograde) through the aortic valve directly into the left ventricle. As more electrophysiologists became engaged with WiSE CRT a venous, transseptal alternative came into favour, largely as a result of familiarity from atrial fibrillation treatments where this approach to the left ventricle is routine.

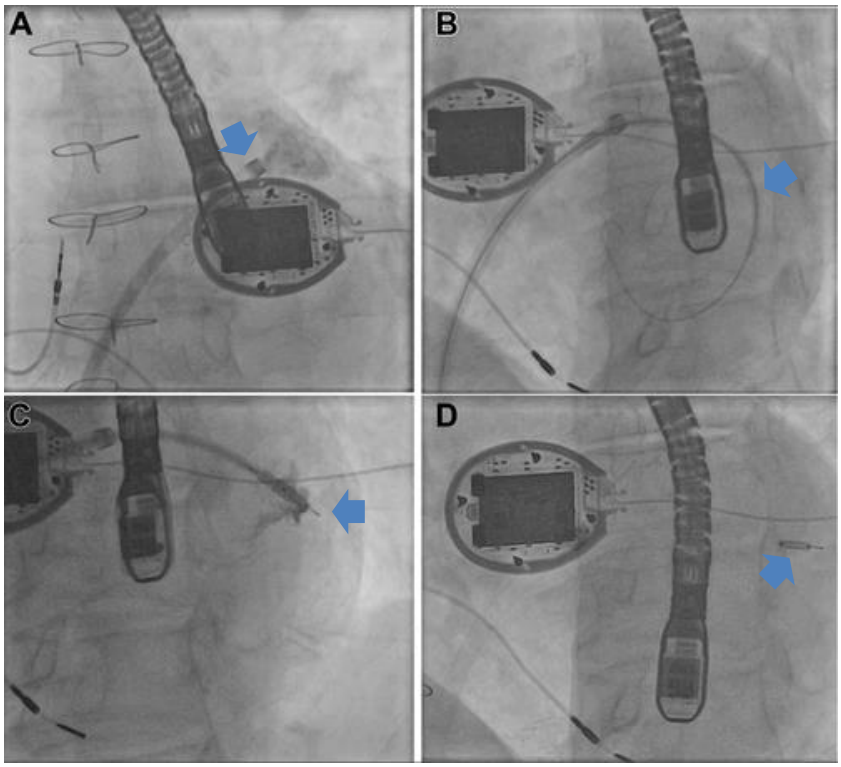
Sieniewicz (2017)[27] describes the transseptal procedure in a case report where the patient was not a candidate for arterial access because both their major vessels were occluded. Accessing the femoral vein proved feasible allowing the introduction of a transseptal needle to punch through from the right atrium into the left and prepare a conduit through which the WiSE delivery catheter could be introduced across the mitral valve. This resulted in excellent electrical resynchronisation (**Figure A11**). The patient was discharged without complication

Figure A10. Venous, transseptal catheter delivery to the LV.



Source: Mt Sinai Hospital

Figure A11. Transseptal deployment of WiSE CRT electrode.



Source: Sieniewicz (2017)[27]

A: atrial septum is identified and a puncture is made via a catheter/needle (arrow).

B: a guidewire is introduced via the catheter and passed across the breached septum (arrow).

C: WiSE delivery system, pre-loaded with the electrode is passed across the septum and implanted in the lateral wall of the left ventricle (arrow).

D: the delivery system catheter is withdrawn, leaving the WiSE electrode embedded in the endocardium (arrow).

Implant technique. The delivery sheath has a balloon at its distal tip which when inflated forms a seal against the endocardium, once positioned. The electrode is advanced 1 mm at a time under live fluoroscopy until anchoring in the endocardium is confirmed. The delivery sheath and electrode catheter are kept stable and the electrode is detached. Satisfactory placement of the electrode can be seen on fluoroscopy, and pacing checks are undertaken to ensure that there is appropriate RV tracking and biventricular pacing is achieved.

Figure A12. WiSE delivery catheter pre-loaded with electrode component



Source: EBR

[27] Sieniewicz, B. J. et al. (2017) *Transseptal delivery of a leadless left ventricular endocardial pacing* electrode J. Am. Coll. Cardiol. EP 3: 1333 – 1335.

A3.2 WiSE evidence review

A3.2.1 Early feasibility studies

We have limited our evidence review to clinical studies in human patients. Select references describing EBR's foundational work in animal models and very early feasibility in human subjects are referenced in Table A4 below but presented without analysis or commentary. In this appendix our goals are to evaluate larger feasibility and efficacy trials and available real-world data with four objectives:

- Validate our understanding of the indications for WiSE CRT as they form a basis for initial forecasting and valuation;
- Benchmark WiSE's clinical performance (safety and efficacy) in those patient groups versus successfully treated candidates in conventional CRT trials and clinical experience;
- Analyse the 'pivotal' SOLVE-CRT trial as the evidentiary basis for Pre-market Approval (PMA) application, including the study design changes made as a result of the COVID-19 pandemic; and finally,
- Review current EBR-sponsored and investigator-led research investigations that may expand indications for WiSE CRT in the future.

Table A4. Selected references to early feasibility studies in animal models and human subjects

Study	Synopsis
Echt *et al.* (2006) [28]	Early feasibility study testing ultrasound-mediated electrical pacing in a pig model (5 treated, 1 sham). Direct and ultrasound-mediated pacing was demonstrated at sites within the RV, RA and LV. Biventricular pacing was also demonstrated in the animals.
Lee *et al.* (2007) [29]	This study was the first-in-human demonstration that an ultrasound transmitting transducer could transmit to a receiver electrode placed in the heart via catheter. Twenty-four patients were enrolled allowing 80 pacing sites to be characterised in terms of transmit-to-receive distances, mechanical index pacing and capture thresholds.
Lee *et al.* (2009)[30]	A 10-patient feasibility study characterising the acoustic window and its effect on transmission between transducer and LV electrode.
Echt *et al.* (2010)[31]	A goat study assessing the safety of chronic electrode implantation. Electrodes were endothelialised at 90 days and no thrombus was present at any time point.

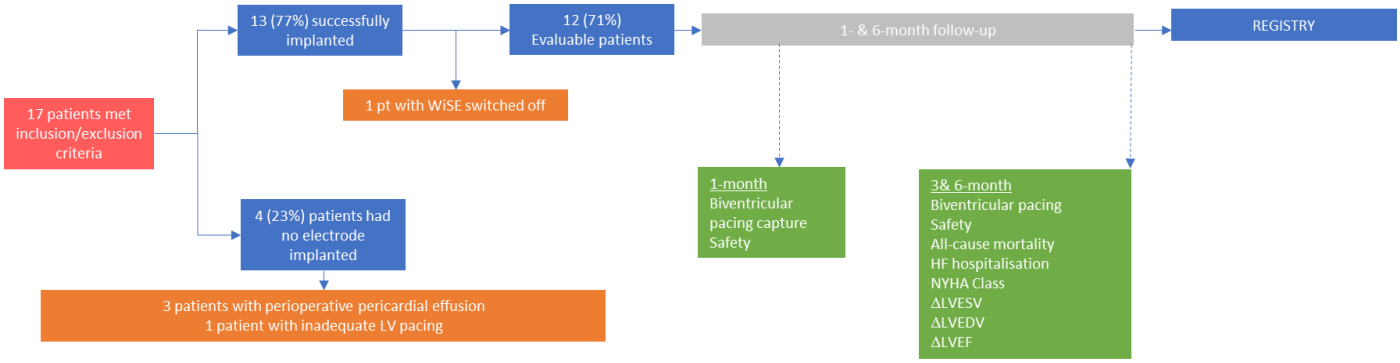
Source: as referenced, Wilsons

The WiSE CRT trial[32] (Wireless Stimulation Endocardially for CRT) was the first feasibility, safety and short-term evaluation study in humans. The WiSE CRT study initially set out to enrol 100 patients in up to 12 centres in Europe. Ultimately the trial enrolled just 17 patients and implanted 13 before being permanently suspended. The decision to halt the trial came after three cases encountered a similar, serious complication: that of pericardial effusion (fluid build-up surrounding the heart) during the electrode implantation procedure. These individual cases are discussed at length later in this section.

The primary endpoint for WiSE CRT was to show functional evidence of biventricular pacing at one month after the procedure. The safety endpoints examined device-related complications within 24 hours and 1 month of implantation. Secondary endpoints characterised device safety and performance at 6 months. Efficacy signals were assessed as secondary endpoints including a change in clinical composite score (CCS – comprising all-cause mortality, HF exacerbation leading to hospitalisation, NYHA functional status and a global patient assessment at 6 months' follow-up). Changes to anatomical structure and electrical remodelling were also assessed using echocardiography, including changes in left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and left ventricle ejection fraction (LVEF) at 6 months. As would be the case in future studies (SELECT and SOLVE) the main clinical point being made in this trial was that WiSE CRT could replicate the benefits enjoyed by CRT responders – but to do so in CRT-refractory/ineligible patient groups.

[28] Echt, D. S. *et al.* (2006) *Feasibility and safety of a novel technology for pacing without leads* J. Heart Rhythm doi:10.1016/j.hrthm.2006.06.012
[29] Lee, K. L. *et al.* (2007) *First human demonstration of cardiac stimulation with transcutaneous ultrasound energy delivery: implications for wireless pacing with implantable devices* JACC 50: 877 – 883.
[30] Lee, K. L. *et al.* (2009) Temporary leadless pacing in heart failure patients with ultrasound-mediated stimulation energy and effects on the acoustic window Heart Rhythm doi: 10.1010/j.hrthm.2009.02.025
[31] Echt, D. S. *et al.* (2010) *Chronic implantation of leadless pacing electrodes in the left ventricle of a goat model* Heart Rhythm 31st Annual Scientific Sessions.
[32] Auricchio, A. *et al.* (2014) *Feasibility, safety and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronisation in heart failure patients: results of the Wireless Stimulation Endocardially for CRT (WiSE CRT) study* Europace doi:10.1093/europace/eut435

Figure A13. Trial schematic for WiSE CRT study



Source: Auricchio et al (2014)[32], Wilsons

WiSE CRT implantation provided or restored CRT benefits to patients who had failed CRT. Patients were eligible if they satisfied the standard indication for CRT (see **Appendix A1**). As the first major feasibility study conducted with WiSE it is unsurprising that the patients enrolled were towards the severe end in terms of symptoms at baseline: predominantly NYHA Class III (with a few Class IVs); a high proportion with ischemic heart insult in their clinical history; very low LV ejection fractions; profound electrical dyssynchrony with ~180 ms QRS intervals (average calculated in the non-pacemaker dependent patients). The indications for WiSE candidacy in this study included 7 patients deemed untreated due to a failed CS lead cannulation or lead instability; 8 patients in need of an upgrade to biventricular pacing but where CS placement was considered too risky; and two profoundly unresponsive patients (functional CRT device installed with no clinical benefit after two years).

Safety – what to take away from a halted feasibility study. Bearing in mind that at this point in WiSE's history the device was only a few years out of animal models, adverse complications – even deaths, were probably inevitable. Of the three pericardial effusion cases reported, one patient died from consequential cardiac tamponade[33]. Case reviews concluded that all of these situations mapped back to the guide wires and catheters used to access the LV. Any and all association with anchoring the electrode in the endocardium was ruled out. Although this was a very small sample size, the rates of serious procedural complications and death were no better or worse than that seen in the formative stages of CRT development[34]. This study provided valuable guidance with respect to the design of steerable catheter/sheath delivery system and procedure. Looking more broadly at serious adverse events (SAEs) in WiSE CRT, there were 19 reported events, of which 7 were judged as procedure-related[35] and not specifically device-related.

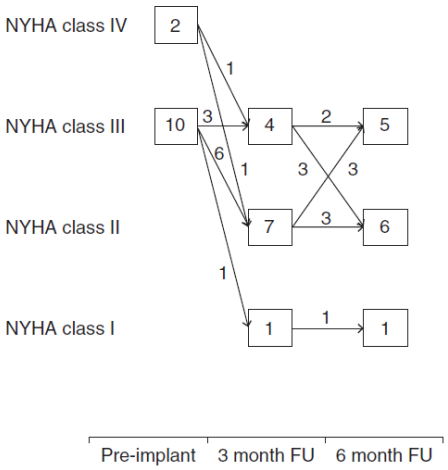
In the 12 successfully implanted patients, device-related safety was encouraging. The most important risk leading into the trial was that of minimising thrombosis. All previous attempts at LV endocardial pacing using conventional leads had been associated with clotting and the requirement for lifelong anticoagulant therapy[36]. WiSE CRT's woven polyester jacket was designed to promote endothelialisation to secure it and present a smooth cellular layer. No thromboembolytic events occurred in this study. There were no cases where the electrode detached nor embolised nor migrated in any way. Notwithstanding the disappointment of the trial suspension, this was the first trial to show that biventricular pacing was feasible in a chronic (rather than acute) sense using WiSE CRT.

[33] Cardiac tamponade is a life-threatening situation where abnormal amounts of fluid accumulate in the pericardial sac compressing the heart and leading to a decrease in cardiac output and shock.
[34] van Rees, J. B. et al. (2011) *Implantation related Complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices. A systematic review of randomized clinical trials.* J Am Coll Cardio; 58:995–1000.
[35] As noted above, there were three peri-procedural pericardial effusion events that occurred; one patient death occurred with one of these events. One SAE occurred as a groin haematoma. In two events, a transmitter position revision was needed due to the loss of the biventricular pacing. One battery replacement was performed during one of the transmitter revisions. As noted above, one other battery replacement was needed but not performed.
[36] Kassai, I. et al. (2011) *Diagnosis and management of inadvertently placed pacing and ICD leads in the left ventricle: a multicenter experience and review of the literature.* Pacing Clin Electrophysiol 23:877–83.

Efficacy. Closing the trial early meant the study lost all statistical power but investigators were able to observe consistent efficacy signals across treated patients. At 6 months follow up 8/12 (67%) of patients reported an improvement in subjective global status. Two-thirds of patients achieved at least a 1-point improvement in NYHA functional class with one individual achieving a 2-point change at 3 months and maintaining it at 6 months. The average NHYA improvement at 6 months was -0.83 (**Figure A14**).

More objectively, there was evidence of structural and electrical reverse remodelling in treated patients. LVEF was increased by 6% (absolute terms) at 6 months (p-value < 0.01 using two-sided t-test). Biventricular pacing achieved a ~40 millisecond shortening of the QRS duration and that change reached statistical significance at both 3- and 6-months (again, limited to two-sided t-tests) (**Table A5**).

Figure A14. Change in NYHA functional class at 3- and 6-months (WiSE CRT)



Source: Auricchio et al. (2014)[32]

Table A5. Summary of WiSE CRT trial outcomes.

Study	WiSE CRT
Reference	NCT01294527
n (treated)	17 (12)
Age	69.0 ± 7.1
Male	82%
Baseline characteristics	
Ischemic aetiology	70.6%
QRS interval (ms)	176.0 ± 30.8
NYHA class III	83%
LVEF %	25.6 ± 4.5
Outcome measures at 6 months	
Global status improvement	67% (8 pts)
Global status unchanged	25% (3 pts)
Global status worsened	8% (1 pt)
Change in LVEF %	+6.0% ± 11.0%
Change in QRS interval (ms)	-42.0 ± 29.2
Change in NYHA status (mean)	-0.83

Source: Auricchio et al. (2014)[32]*, Wilsons*

Key development insights gained from WiSE CRT.

First demonstration of sustained biventricular pacing at 6 months. Successful cases achieved LV resynchronisation on par with conventional CRT and that was also objectively evident from reverse remodelling data. The loss of pacing in two patients helped define the acoustic window constraints for WiSE implantation, informing transmitter placement. These results gave investigators the confidence to design a larger study assessing potential indications for WiSE in patients where conventional CRT could not be instigated or had failed (SELECT-LV).

Delivery system re-design. The complications that stopped the trial led to the redesign of the sheath and catheter delivery systems. At this stage WiSE CRT was still being placed using an arterial, retrograde approach but this too began to be questioned following this study.

A3.2.2 SELECT-LV Study

The SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) study was a prospective, multicentre, non-randomised, single-arm study assessing the safety and performance of WiSE CRT in patients deemed to have 'failed' conventional approaches to CRT[37]. The primary endpoint was evidence of biventricular pacing at one month. The safety endpoints examined device-related complications within 24 hours and 30 days of implantation. Secondary endpoints characterised device efficacy.

The main efficacy measure was a change in clinical composite score (CCS – comprising all-cause mortality, HF exacerbation leading to hospitalisation, NYHA functional status and a global patient assessment[38]) at 6 months' follow-up. As in the preceding WiSE CRT study, CCS results were classified as having improved, stayed the same or worsened. Structural changes were also assessed using echocardiography including changes in left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and left ventricle ejection fraction (LVEF) at 6 months.

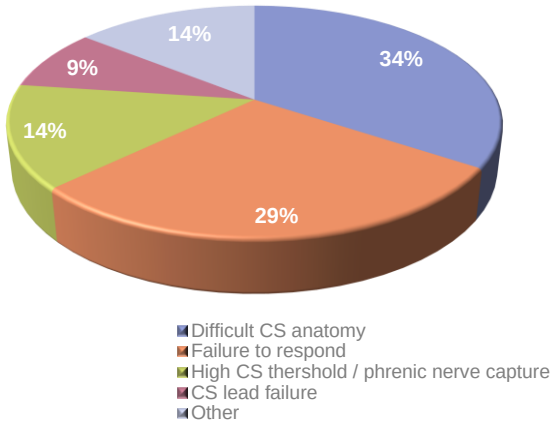
SELECT-LV set out to establish that WiSE CRT implantation could provide or restore CRT benefits to patients who had failed CRT. Patients were eligible if they satisfied the standard indication for CRT (see **Appendix A1**) and at least one of the following criteria:

- Conventional CS lead could not be placed owing to higher perceived infection risk or obstructive venous anatomy;
- Conventional CRT was attempted but failed on account of difficult anatomy or phrenic nerve involvement;
- Conventional CRT was implanted previously with suboptimal or non-responsiveness evidenced by a worsening of NYHA functional status after 6 months of treatment.

These qualifying complications aside, heart failure severity at baseline was reasonably consistent with other conventional CRT trials in terms of functional status (age, NYHA class, ischemic history) and structural heart features (LVESV, LVEF, etc). See **Table A7** overleaf (p.54) for a comparison of patient characteristics and outcomes from selected conventional CRT trials (CRT-treated cohorts only).

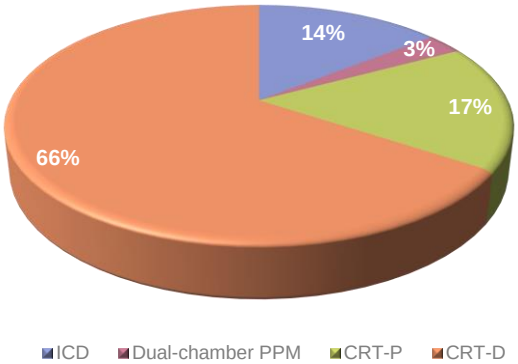
WiSE CRT implantation is agnostic on the choice of co-implant. As a reminder, in its current configuration, the WiSE CRT transmitter detects a pulse from a co-implanted system pacing the right ventricle. Over 80% of patients in SELECT had a defunct CRT-P/D system. Fourteen percent of patients had ICDs and one individual had a dual-chamber pacemaker.

Figure A15. Reasons for failing conventional CRT among candidates enrolled in SELECT-LV



Source: Reddy (2017)[37], Wilsons

Figure A16. WiSE pairs with pacemakers, ICDs and failed CRT-P/D devices. Co-implant mix in SELECT-LV

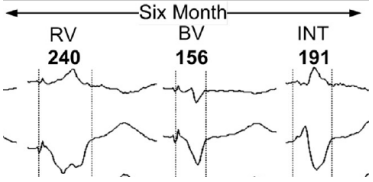


Source: Reddy (2017)[37], Wilsons

[37] Reddy, V. Y. et al. (2017) *Cardiac resynchronisation therapy with wireless left ventricular endocardial pacing* J.Am. College Cardiology 69: 2119 – 2129.
[38] The global assessment score is a 7-point rating scale, allowing for the evaluation of the patient's own perspective of overall health compared with a previous point in time.

Implantation and functional performance. SELECT enrolled 39 patients and implanted 35 of them. Three patients did not undergo a procedure because their anatomy precluded finding an acoustic window between the WiSE transmitter and electrode. One patient withdrew for unrecorded reasons. Of the 35 patients implanted one did not receive the electrode component because of an unrelated arrhythmia during the procedure. SELECT-LV's primary endpoint was a functional, device-related measurement, to demonstrate that the device was achieving biventricular pacing (BV). BV is associated with a shorter QRS duration and this is measured using a standard 12-lead ECG (**Figure A17**). Biventricular pacing was achieved in 33/34 (97%) of successfully implanted patients at one month post-implantation.

Figure A17. Biventricular pacing (BV) is associated with a shorter QRS interval compared to the heart's intrinsic ability (INT) and when paced from the right ventricle only (RV).



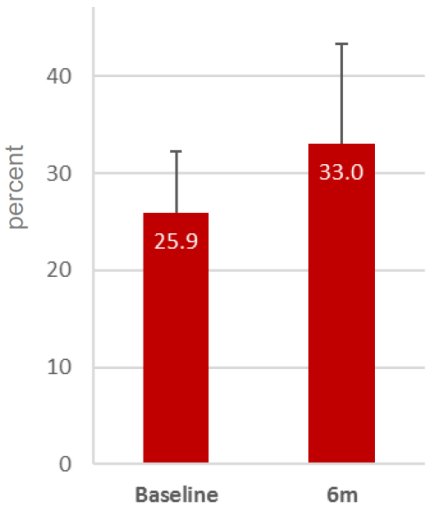
Source: Reddy (2017)[37]

Safety observations. Bearing in mind that the procedural elements of the WiSE procedure were still evolving when SELECT-LV was performed, complication rates were remarkably low. There were 3/35 cases of serious procedural/device-related events including one death[39]. In another patient the electrode embolized to the tibial artery without angiographic occlusion or symptoms. The third patient developed an unrelated femoral artery fistula.

Efficacy signals. SELECT-LV was a single-arm pilot study at best with no formal control arm or randomisation in its design. In an important sense each patient was his/her own control given their recent clinical history of CRT-failure. SELECT-LV demonstrated three clinical points strong enough to warrant progression into a pivotal program:

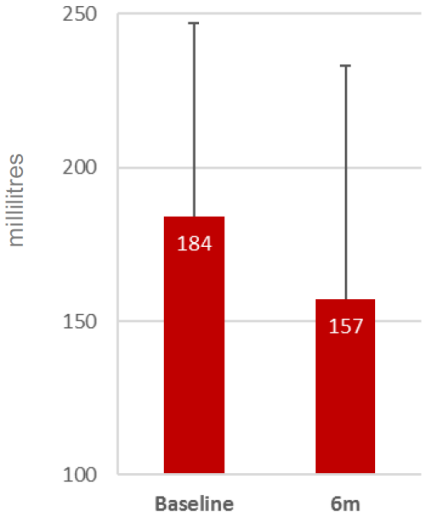
- 85% of patients improved on the composite score endpoint and of those, half were 'markedly' improved;
- An increase in LVEF and decreases in LVESV and LVEDV after 6 months (all changes from baseline with statistical significance). See **Figures A18-A20** below. These changes suggest reverse remodelling in line with previous CRT trials (in responsive patients); and
- Evidence of electrical remodelling where resynchronisation led to a reduction in intrinsic QRS duration which is believed to correlate with clinical response[40] (**Figure A20**).

Figure A18. LV ejection fraction at baseline and 6 months follow up. Delta: +7.1 ± 8.0% (p = 0.001).



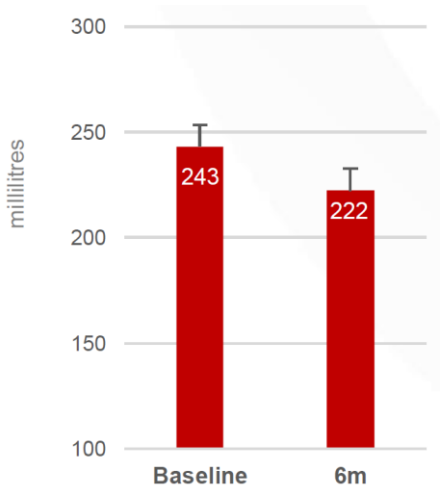
Source: EBR

Figure A19. LV end systolic volume at baseline and 6 months follow up. Delta: -26.8 ± 45.1 mL (p = 0.007).



Source: EBR

Figure A20. LV end diastolic volume at baseline and 6 months follow up. Delta: -20.6 ± 41.4 mL (p = 0.02).

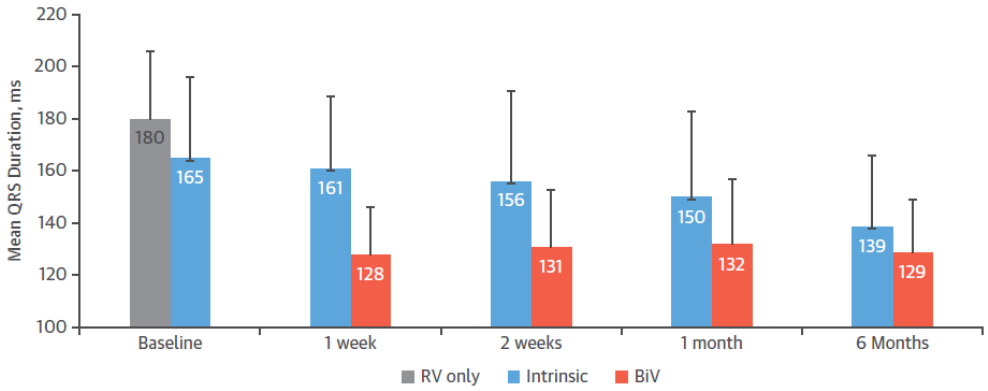


Source: EBR

[39] This patient developed ventricular fibrillation when a delivery catheter contacted the LV endocardium, leading to cardiac arrest. The patient was resuscitated but died 4 days later.

[40] Bonakdar, H. R. et al. (2009) *Prediction of response to cardiac resynchronisation therapy using simple electrocardiographic and echocardiographic tools* Europace 11: 1330 – 1337.

Figure A21. Evidence of progressive electrical remodelling in SELECT-LV. Biventricular pacing is confirmed by a shorter QRS interval (the time between different phases of the heart's contraction process, measured in milliseconds). Data from 20 SELECT-LV patients.



Source: Reddy (2017)[37]

Note: The analyses at left were possible only when patients where not pacemaker dependent (n=20). QRS was measured using a 12-lead ECG in different states. At baseline, QRS was measured with the pacemaker pacing the patient's right ventricle (RV) and with that pacemaker turned off (intrinsic). At each subsequent follow up, QRS was measured with WiSE biventricular pacing turned on (BIV) and programmed off (intrinsic). Over the 6 month period there was a 51 ms (-28%) change in QRS interval compared to baseline.

From a benchmarking perspective the important question is whether the rates and quality of clinical responses observed in SELECT-LV compare with the body of clinical trials that underpin CRT generally. **Table A6** summarises SELECT-LV alongside data from the interventional arms of four CRT trials: PROSPECT[41], MIRACLE[42], REVERSE[43] and MIRACLE ICD[44].

Briefly on the comparator studies: a) PROSPECT was a prospective, non-randomised study in which 69% of patients improved on CRT but found no single ECG measure of dyssynchrony stood out as a reliable predictor of CRT response; b) MIRACLE and MIRACLE ICD were foundational, randomised, double-blind trials that helped established the CRT indication in the early 2000s; and c) REVERSE was a more recent RCT which looked primarily at earlier stage heart failure patients (i.e NHYA Class II) showing a 68% reduction in mortality in patients with ≥15% decrease in LSESVi. All of the efficacy outcomes examined in SELECT-LV compare favourably with these trials. On the CCS endpoint we note the low proportion of unchanged/worsening patients. Reductions in LVESV at 6 months are broadly in line; as are absolute improvements in LVEF and NHYA classification (refer **Table A6** overleaf).

[41] Chung, E. S. *et al.* (2008) *Results of the Predictors of Response to CRT (PROSPECT) trial.* Circulation 117: 2608 – 2616.
[42] Abraham, W. T. *et al.* (2002) *Cardiac resynchronisation in chronic heart failure* NEJM 346:1845 – 1853.
[43] Gold, M. R. *et al.* (2015) *The effect of reverse remodelling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronisation therapy: Results of the REVERSE study* Heart Rhythm 12: 524 – 530.
[44] Young, J. B. *et al.* (2003) *Combined cardiac resynchronisation and implantable cardioversion defibrillation in advanced chronic heart failure* JAMA 289: 2685 - 2694

Table A6. Summary of SELECT-LV trial outcomes compared with historical outcomes in subjects from comparable CRT studies

Study	SELECT-LV	PROSPECT	MIRACLE	REVERSE	MIRACLE ICD
Modality	WiSE CRT	CRT	CRT	CRT	CRT ICD
n (evaluable treatment group)	35	426	228	353	142
Age	65.4 ± 7.9	67.8 ± 11.0	63.9 ± 10.7	63.0 ± 10.6	66.6 ± 11.3
Male	85%	71%	68%	77%	76%
Baseline characteristics					
Ischemic aetiology	42.9%	54%	50%	57%	64%
LVESV (mL)	184 ± 63	168 ± 89	NR	99.4 ± 34.7‡	NR
NYHA class III	73%	96%	90%	19%†	89%
LVEF %	26.0 ± 6.2	23.6 ± 7.0	21.8 ± 6.3	26.8 ± 7.0	24.2 ± 6.5
Outcome measures					
CCS - Improved	85%	69%	67%	54%	52%
CCS - Unchanged	9%	15%	17%	30%	15%
CCS - Worsened	6%	16%	16%	16%	33%
LVESV reduction ≥15%	52%	56%	NR	52%	NR
Reduction in LVESV at 6 months (mL)	26.8 ± 45.1	33.1 ± 45.9	NR	14.9 ± 27.5‡	22.2 ± 21.8
Relative reduction in LSESV (%)	14.6 ± 24.5	19.7 ± 27.3	NR	15.0 ± 27.7‡	NR
Absolute improvement in LVEF %	7.1 ± 8.0	NR	4.6 ± 4.8	NR	2.1 ± 2.7
Point improvement in NYHA status	0.8 ± 0.8	NR	0.8	NR	~1.0

CCS = clinical composite score a primary endpoint comprising all-cause mortality, HF hospitalisation, NYHA functional class and global patient assessments at 6 months.
NR: not reported
† REVERSE enrolled 81% NYHA Class II patients; ‡ REVERSE reported on an LVESV index basis in units of mL/m²
Source: as referenced, Wilsons

Key development insights gained from SELECT-LV.

SELECT-LV formed the basis for WiSE CRT's CE Mark in 2015. CE Mark allows marketing of WiSE (in relevant European countries) for three indications in CRT-eligible patients:

- Who are non-responders to CRT; or
- where LV lead deployment is not possible or had failed (anatomical constraints, high capture thresholds, prhenic nerve stimulation); or
- undergoing CRT upgrade but implanting an LV lead is impractical due to poor venous access or previous pocket infection.

Clarified the breadth of WiSE CRT patient eligibility and indications for US pivotal trial. Subgroup analysis in patients presenting as high-risk upgrades or with lead failures (both acute and chronic) with acute lead failures had a 19.9% reduction in LVESV (versus 14.6% assessed over the broader study). This analysis included 18/35 patients. These indications were selected for further investigation in the randomised controlled component of the SOLVE pivotal trial.

Limitations of retrograde arterial approach. Although implantation success was 97% in SELECT-LV the method of electrode deployment used (retrograde arterial) has been outmoded. The arterial side of the circulatory system is under higher pressure and more prone to obstruction (e.g. atherosclerosis). Moving the deployment approach across to the venous anatomy has another advantage in that electrophysiologists (likely to become the medical speciality that embraces WiSE) already possess the skills and experience related to this deployment technique.

Acoustic window exclusion rate of 7.7%. 3/39 planned WiSE procedures could not be completed because the patient's anatomy and electrode placement did not align. The location for the transmitter needs a lung and bone-free line of site to where the electrode is placed in the LV endocardium. For most patients this was achieved by implanting the transmitter between the 4th and 6th intercostal spaces (ribs) and just to the left of the sternum. SELECT-LV may have benefited from strategies to optimise electrode site selection and transmitter position concurrently.

Thromboembolism risk yet to be properly characterised. The necessity for long term anticoagulant therapy in WiSE recipients is unknown. We understand that successfully treated SELECT-LV patients were enrolled in the ongoing WiSE Registry which will shed light on this in time (see **A3.2.3**).

A3.2.3 Real world evidence (Post Market Surveillance Registry) confirms performance with longer term safety data planned.

Following CE Mark in 2015 EBR initiated a multicentre international registry to capture longer term, real world clinical experience, safety and outcomes data. The study was initiated in February 2016 and set out to enrol 100 patients at three centres in Germany, Denmark and Switzerland. Inclusion criteria were consistent with CE Marked indications[45]. Planned follow-ups were at 1 week, 3 months, 6 months, 12 months and then annually out to 5 years post-implantation. Earlier this year investigators involved in the registry published results from 90 patients implanted at 14 centres[46].

Endpoints. Three safety and efficacy assessments were prespecified:

- Procedural success including the confirmation of biventricular pacing using ECG;
- Safety including acute (24 hours), intermediate (24 hours–1 month), and long-term (1–6 months) complications.
- Clinical response assessing the proportion of patients who experienced improvement in clinical symptoms 6 months after implantation (CCS basis, consistent with both WiSE CRT and SELECT-LV). This simple global assessment of symptoms classified each patient into 1 of 3 categories: improved, worsened, or unchanged.

Patient characteristics and WiSE indications. As a group, the registry patients had slightly less HF severity compared with those enrolled in SELECT-LV on the basis of both symptoms (NYHA classification) and structural characteristics (smaller LV volumes, more forceful ejection capability). The range and mix of indications within the registry was reasonably consistent with SELECT-LV (lead failures v. upgrades v. non-responders).

Table A7. Patient characteristics for Registry and SELECT-LV studies compared.

	Registry	SELECT
n	90	35
Age (yrs)	68.2 ± 10.5	65.4 ± 7.9
Male (%)	72 (80.0)	29 (82.9)
Ischemic aetiology	36 (40.0)	15 (42.9)
NYHA Class		
I	1(1.1)	1(3)
II	33 (36.7)	8 (24)
III	56 (62.2)	26 (73)
IV	0 (0)	0 (0)
Echocardiographic status		
LVEF (%)	30.6 ± 8.9	25.9 ± 6.4
LVESV (mL)	130.4 ± 78.5	183.8 ± 62.9
LVEDV (mL)	185.7 ± 93.0	243.1 ± 70.7
Indication		
Failed LV lead implant	44 (48.9)	8 (22.9)
Complex upgrade	34 (37.8)	12 (34.2)
Failed to respond to CRT	12 (13.3)	10 (29.0)

Source: Sieniewicz et al. (2020)[46]; Reddy et al. (2017)[37]; Wilsons

Safety observations. Device/procedural-related adverse events occurred in a significant number of patients but was broadly consistent with that observed in the SELECT-LV trial. Nearly 80% of complications occurred within a centre's first 10 cases, suggesting a learning curve effect. Electrode deployment via the arterial route was still primarily via the retrograde, aortic route which today is almost never used. There were three deaths associated with the procedure. In two cases the root cause was tamponade (perforations during electrode placement). The third death was from sepsis of unknown origin.

[45] https://clinicaltrials.gov/ct2/show/NCT02610673
[46] Sieniewicz, B. J. et al. (2020) *Real-world experience of leadless left ventricular endocardial cardiac resynchronisation therapy: a multicentre international registry of the WiSE CRT pacing system* Heart Rhythm 17: 1291 – 1297.

Symptomatic and reverse remodelling efficacy. Consistent with previous studies, the echocardiographic assessment of LV reverse remodeling six months after implantation was key. As was the case in SELECT-LV, patients were considered responders if they exhibited a ≥ 15% reduction in LVESV. Only 43 patients were evaluable on this basis (**Table A8**) with 14 excluded (failure to achieve stimulation, death or loss to follow-up) and 33 where the analysis was not conducted. LV ejection fraction increased from 30.6% ± 8.9% at baseline to 37.0% ± 11.5% at six months. LVEDV decreased from 185.6 ± 93 mL to 161.0 ± 83.3 mL whilst LSESV decreased from 130.4 ± 78.5 to 107.0 ± 71.6 mL. Using the pre-specified endpoint of ≥ 15% reduction in their LVESV, 54.5% of patients were deemed echocardiographic responders (recall 52% response rate in SELECT-LV and across the four *de novo* CRT trials summarized in **Table A6**).

Table A8. LV reverse remodelling data (n=43) in real world cohort

Parameter	Baseline ± SD	6 Months ± SD	P value	Response Definition	Response Rate at 6 Months
LVESV (ml)	130.4 ± 78.6	107.0 ± 71.6	<0.0001	> 15% relative reduction	54.5%
LVEDV (ml)	185.6 ± 93.0	161.0 ± 83.3	<0.0001		
LVEF (%)	30.6 ± 8.9	37.0 ± 11.5	<0.0001		
QRS (ms)	180.7 ± 27.0	136.2 ± 84.3	<0.0001		
NYHA	2.6 ± 0.5	2.1 ± 0.7			

Source: Sieniewicz (2020)[46], Wilsons

Key development insights gained from the WiSE registry study.

Robust results across multiple European sites. The registry took cases from 14 centres including only 3 of those that had been involved in SELECT-LV. It also expanded use into several new countries: UK, Ireland, France, Denmark and Italy. The learning curve phenomenon (80% of complications occurred in earlier cases) was not surprising and informed the inclusion of a 'run-in' phase for EBR's pivotal SOLVE trial which is reviewed in the next section.

Long term follow-up expected in coming years. The registry is the first observational study set up to report formally on complication rates and functional performance (biventricular capture) out to 5 years. The only pre-specified measure of symptomatic and physiological outcomes (including mortality) was at 6-months (as reviewed in this section).

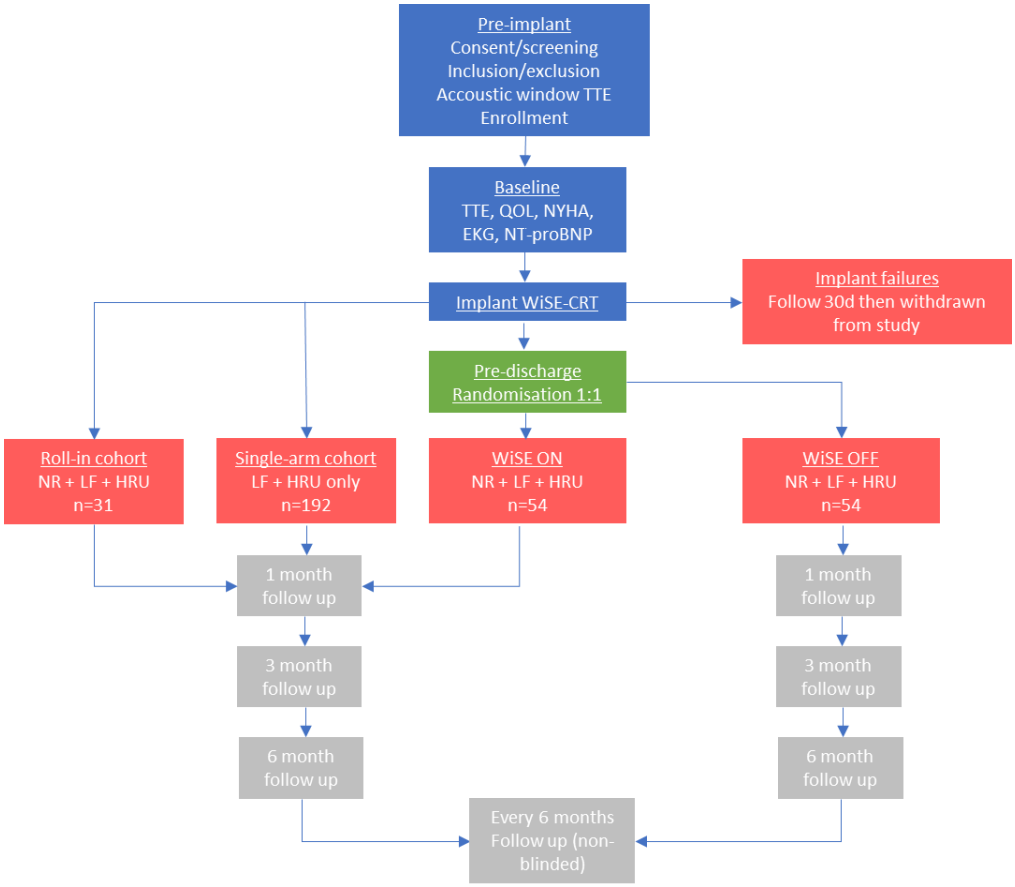
A3.2.4 SOLVE-CRT pivotal program

SOLVE-CRT was originally conceived as an international, multicentre, randomised, double-blind, sham-controlled trial. SOLVE's planned enrolment target was 350 patients (Class I and IIa indications for CRT who have failed to respond or have been unable to receive conventional CRT). The primary safety endpoint was to achieve >70% freedom from complications caused by WiSE CRT system components or procedure-related vascular events, stroke, pericardial effusion or surgical pocket infections. The primary efficacy endpoint had three components, all of which needed to be satisfied:

- Absolute change in LVESV at 6 months, hypothesising that patients randomised to the ON group will have greater reductions in LVESV (trial designed on the basis of a 22.5 mL reduction in volume recalling that SELECT-LV reported a reduction of 26.8 ± 45.1 mL);
- The proportion of patients with an LVESV reduction ≥ 15% - expecting treated patients to exhibit a more favourable distribution of outcomes (design basis is for control/sham group to have a response rate of 15% and for WiSE to outperform that by ≥ 20%); and
- A clinical composite score including NHYA classification, quality of life questionnaire, all-cause mortality, HF exacerbations (designed on the basis of 55% and 40% response rates in treated and control/sham groups, respectively – SELECT-LV patients achieved an 85% response rate).

SOLVE-CRT was the centrepiece of EBR's successful FDA application to trial WiSE CRT in the USA under an Investigational Device Exemption (IDE). Following COVID-19 related disruptions, the trial design was reconfigured as shown in **Figure A22** below and discussed in the following pages.

Figure A22. Respecified SOLVE-CRT trial schematic



TTE = transthoracic echocardiogram; QOL = quality of life; NYHA = New York Heart Failure Association; EKG = electrocardiogram; NT-proBNP = B-type natriuretic peptide; NR = non-responders; LF = lead failures (acute and chronic); HRU = high risk CRT upgrade.

Source: EBR, Wilsons

SOLVE redesigned after COVID-19 pause. SOLVE started recruiting its 'roll-in' patients in early 2018[47]. A 31-patient roll-in phase was completed and the results were published (reviewed later in this section on p.58). The pivotal, randomised component of the trial enrolled 108 patients before the trial was paused in early 2020. After consultation with FDA the design was changed, specifying a final single-arm, treatment only cohort of up to 192 patients with an interim analysis for potential early stopping.

Redesigned single-arm cohort avoids a pivotal trial re-do, offers a simpler efficacy endpoint but at the expense of indication breadth. SOLVE's original design as a simple RCT comparing device ON to device OFF (sham) was beyond reproach as far as following the industry standard in CRT. EBR has worked pragmatically with FDA to salvage an approvable dataset. To be clear, the revised design falls within the mandate of an approved IDE and as such, is potentially sufficient for PMA approval if the results are supportive. In that sense, EBR was able to preserve a timeline for potential FDA approval in 2H 2023 (assuming interim look is positive) rather than starting afresh. The primary efficacy endpoint for the 192 patient single-arm component has been limited to the mean percentage (relative) change in LVESV from baseline to 6 months. The primary safety endpoint remains unchanged: less than 30% of patients experiencing device- or procedure-related complications. Importantly though, FDA required that non-responding patients be excluded from this last phase of the study. FDA took the view that the evaluation of such patients would require a randomised design. As such, the revised SOLVE will not support FDA approval in non-responders.

Proposed indications. Assuming positive results from SOLVE, EBR's anticipated PMA indications are:

- **Acute lead failures (LF)** – patients who have a CRT indication but who are unable to have the lead implanted in their CS due to their anatomy or disease condition;
- **Chronic lead failures (LF)** – patients with an implanted CRT device that has had the CS lead switched off or the lead has become otherwise ineffective due to the lead failing or not functioning properly, or causing unwanted (phrenic nerve) stimulation; and
- **High Risk Upgrade (HRU)** – patients with an existing pacemaker or ICD implant who subsequently develop heart failure requiring CRT but who have a high risk of potential complications from upgrading to a conventional, lead based CRT system.

Endpoint performance targets. EBR has provided subgroup analyses from published data assessing the revised efficacy endpoint (percentage LVESV changes from baseline at 6 months) from within previous studies. Pooled efficacy across trials shows a >2-fold safety margin versus the targeted LVESV reduction of 9.3%. To be consistent, we pool safety data from the same trials. The pooled result is just in line with the SOLVE target of 70% but note that that complication rates have improved dramatically in the years that separate the SELECT-LV and SOLVE-CRT trials.

Table A9. SOLVE efficacy and safety goals achieved in previous trials

Primary efficacy endpoint	LF & HRU subgroup (total pts)	% Δ LVESV
SOLVE roll-in study	15/31	-18.5%
SELECT-LV	18/35	-19.9%
Post Market Surveillance Registry	47/90	-20.9%
Pooled Results	80/156	-20.2%
SOLVE endpoint goal		-9.3%
Primary safety endpoint	**Pts**	**% free of complications (6m)‡**
SELECT-LV	35/35	71.4% (25/35)
Post Market Surveillance Registry	90/90	82.2% (74/90)
SOLVE roll-in study	31/31	90.3% (28/31)
Pooled Results	156/156	81.4% (127/156)
SOLVE endpoint goal		70%

‡ includes Type 1 complications only (as those caused by a component of the investigational device (WiSE CRT system transmitter, battery, electrode, catheter, sheath, and/or programming software), or specific procedure-related events including vascular events, stroke, pericardial effusion, and pocket-related events.
Source: trials as referenced, EBR, Wilsons

[47] Okabe, T. et al. (2021) *Leadless left ventricular stimulation with WiSE CRT System – Initial experience and results from phase I of SOLVE-CRT Study (nonrandomized, roll-in phase)* Heart Rhythm ul 23;S1547-5271(21)01808-7

Reviewing SOLVE's roll-in component. This component of the trial was done in new centres with limited prior experience with WiSE CRT implantation. All physician investigators underwent training (didactic lecture, animal lab, and battery/transmitter implantation on cadavers). All 31 patients were successfully implanted and 30 completed 6-month follow-up[48]. Sixteen patients were lead failures or upgrade patients and 15 were non-responders.

Safety. Investigators reported only three complications (9.7%) and no cardiac tamponade events or deaths. One patient experienced inadequate pacing capture. The most serious complication was embolization of the electrode to the femoral artery which was retrieved and replaced. The final complication described was a wound infection six weeks post-implant which resolved on antibiotic therapy. There were five non-Type I cardiopulmonary complications related to the procedure.

Efficacy. **Table A10** below summaries the structural changes at 6 months from baseline. Although significant in paired t-test terms this component of SOLVE had no comparator group and spontaneous improvement post-implantation cannot be ruled out. All patients were aware that their WiSE CRT system was turned on. Forty-seven percent of patients demonstrated ≥1-point improvement in NHYA classification.

Table A10. Summary of SOLVE trial outcomes compared with historical outcomes in subjects from comparable CRT studies

LVEF (%)		LVEDV (mL)		LVESV (mL)	
Baseline	6 months	Baseline	6 months	Baseline	6 months
Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
[min, max]	[min, max]	[min, max]	[min, max]	[min, max]	[min, max]
28.3 ± 6.7	33.5 ± 6.9	185.4 ± 58.8	164.9 ± 50.6	134.9 ± 51.3	111.1 ± 40.3
[13.7, 43.0]	[16.0, 51.9]	[65.0, 377.0]	[67.0, 270.0]	[45.0, 325.0]	[42.0, 192.0]
Δ = 5.2 ± 5.8		Δ = -20.5 ± 31.9		Δ = -23.7 ± 31.7	
p < 0.001		p = 0.0017		p = 0.0004	

Source: Okabe et al. (2021)[47], Wilsons

Interim analysis results expected 2H 2022. A pre-specified interim analysis is planned at 75/192 patients in the final single-arm component. The decision structure at that point is as follows:

- Analysis on the primary efficacy endpoint (mean percentage change in LVESV from baseline at 6 months).
- Analysis on the primary safety endpoint. If safety and efficacy significance is met at this stage the trial may be closed early.
- If the result is underpowered at this stage SOLVE-CRT will go on to enroll the remaining 117 patients.

RCT component may be under-powered as a result of scaling down. We assess that the re-specified RCT component of SOLVE is likely underpowered at n = 108. Under the original design, the trial was powered at 90% to detect a 22.5 mL difference in LVESV between the active and sham groups (alpha = 0.025 using one-sided, two-sample t-test). We calculate that this trial would only reach significance if there was a ~35 mL difference between the groups at this smaller n (assuming sample standard deviations of 50%).

[48] One patient left the study for heart transplantation and was excluded.

A3.3 Investigator led indication expansion

A3.3.1 Indication expansion via supplementary filings and real-world data.

Whilst EBR's proposed initial FDA indication excludes non-responders we would expect to see the device used in this indication off-label given the preponderance of previous trial and real-world data in this setting. EBR may contemplate a formal program of additional studies to support supplementary PMA extension. Equally, as experience with upgrade patients develops there may be opportunities to expand this usage to lower risk cohorts.

A3.3.2 Opportunities in completely leadless CRT

Leadless upgrade patients: patients who already have a leadless pacemaker in their right ventricle but have developed heart failure and need to upgrade to CRT. Medtronic's transcatheter, leadless pacing system Micra is growing strongly within its approved indications and following last year's approval of the dual-chamber version (Micra AV). Micra systems are indicated for:

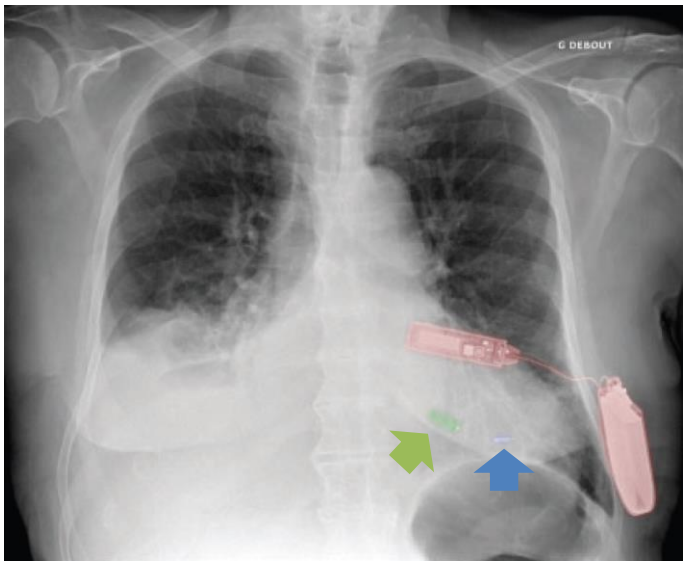
- Symptomatic paroxysmal or permanent high-grade AV block in the presence of AF;
- Symptomatic paroxysmal or permanent high-grade AV block in the absence of AF as an alternative to dual chamber pacing when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy;
- Symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia/sinus pauses), as an alternative to atrial or dual chamber pacing when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.

Medtronic's Micra devices are implanted in the right ventricle and are leadless – thus obviating certain mechanical thrombotic complicating and infectious risks. WiSE CRT is the only option for upgrading these leadless patients once they develop a requirement for biventricular pacing (e.g. 15% of patients with high RV pacing burden could develop pacemaker-induced heart failure[49]). We estimate that Micra-related upgrades could support a US$75-100M sales market for WiSE by 2030.

Clinical experience pairing Micra (single chamber) and WiSE CRT. Two early case reports in 2019 showed that fully leadless pacing with WiSE/Micra was feasible[50,51]. This year an 8-patient multicentre study reported preliminary data describing the safety of the combination[52]. From this series, 7/8 patients reached 6 months follow up. One patient died from an acute heart failure exacerbation (not related to the study devices). As a small study with no comparator arm only two functional metrics achieved significance. QRS duration was reduced by 66 ms after WiSE was switched on (**Table A11**) and remained lower after 6 months follow-up (the mean QRS duration improved by another 13 ms but that additional change was not statistically significant). LV ejection fraction did improve significantly for these patients but there was no evidence of reverse remodelling. The trend changes in LVEDV and LVESV moved in a positive way but the small n and variability precluded significance

Patient baseline characteristics suggests that these patients had slightly better functional and structural status than those enrolled in the SOLVE-CRT roll-in or European registry cohorts.

Figure A23. Patient chest X-ray. Red: WiSE CRT subcutaneous battery and ultrasound generator. Blue: WiSE CRT electrode. Green: Micra leadless pacemaker.



Source: Carabelli (2021)[52]

[49] Dreger, H. *et al.* (2012) Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. Europace 14:238–42.
[50] Montemerlo E. *et al.* (2019) First-in-man fully leadless transvenous CRT-P with a transseptal implant of WISE CRTVR system and MicraVR PM. Pacing Clin Electrophysiol 42:1489–92.
[51] Funasako M. *et al.* (2020) Successful implementation of a totally leadless biventricular pacing approach. Heart Case Reports 6:153–7.
[52] Carabelli, A. *et al.* (2021) *European experience with a first totally leadless cardiac resynchronization therapy pacemaker system* Europace 23: 740 – 747.

Table A11. Summary efficacy measures from WiSE/Micra combination leadless CRT (European case series)

LVEF (%)		QRS duration (ms)		LVESV (mL)	
Baseline	6 months	Baseline	6 months	Baseline	6 months
Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
28.4 ± 8.0	39.7 ± 11.9	204.4 ± 30.3	137.5 ± 24.8	117.3 ± 35.6	91.9 ± 48.4
Δ = 11.3 ± 8.5		Δ = -66.9 ± 31.6		Δ = -23.0 ± 27.8	
p = 0.018		p = 0.012		p = 0.24	

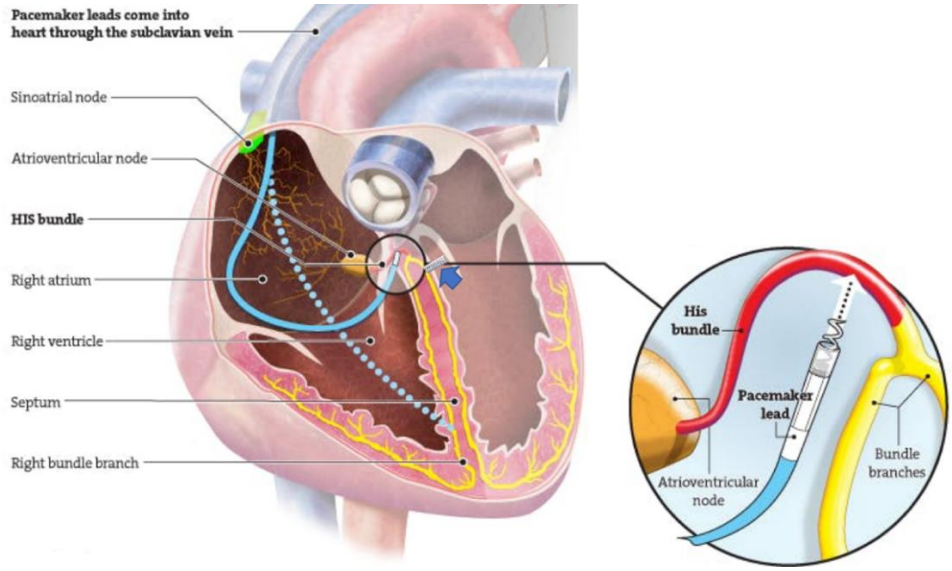
Source: Carabelli (2021)[52], Wilsons

A3.3.3 Opportunities in conduction system pacing (CSP)

Feasibility of leadless left bundle branch area pacing (LBBAP). Conduction system pacing (CSP) is an alternative strategy for providing CRT. Conventional biventricular pacing (using CRT leads and even WiSE when implanted endocardially in the LV wall) work by delivering non-physiological wavefronts to the left ventricle in an effort to resynchronise it with the right ventricle. CSP aims to place leads directly into the intrinsic, electrically conductive tissue that links right and left. This approach hopes to provide a more authentic mimic of physiological pacing. WiSE CRT is the only leadless system with the potential for CSP. Recently, investigators published the first case where this was achieved.

Commercial significance – WiSE CRT indication expansion to first line. LBBAP has potential to replace conventional CRT pacing in first line because physiological pacing is associated with superior electrical resynchronisation and faster LV activation time. Additionally, CSP overcomes common 'blocks' to conventional biventricular pacing: such as left bundle branch block (LBBB) and atrioventricular block. Applications also include traditional bradycardia and atrial fibrillation.

Figure A24. WiSE electrode (blue arrow) implanted in the LV aspect of the septum to provide left bundle branch area pacing (LBBAP). Lead systems have attempted to pace from His bundle and LBBAP from the RV.



Conduction system pacing using conventional leads can target either the His bundle (HBP) or in the left bundle branch area (LBBAP). HBP and LBBAP have both attracted attention as alternatives to conventional CRT – particularly in patients where electrical communication between the right and left side of the heart is blocked. HPB recently was included on European Society of Cardiology (ESC) guidelines as an option for CRT candidates in whom CS lead implantation is unsuccessful (Class IIa recommendation).

Source: University of Minnesota, Wilsons

Case reports. Physicians at St Thomas' Hospital (London) and Grenoble Alpes University Hospital published two cases[53]. The first case explored a temporary placement only but showed that pacing from the LV aspect of the intraventricular septum achieved greater electrical resynchronisation compared to pacing from the mid-lateral LV wall. The second patient had the WiSE electrode implanted permanently in the left aspect of the septum (placed using a transseptal approach from the right atrium). WiSE significantly improved electrical resynchronisation (QRS duration was 142 ms during biventricular pacing and 207 ms with RV pacing alone. At six months follow up device function was satisfactory with symptomatic improvement (1-point improvement on NYHA scale).

EBR study plans. We understand that clinical investigators are planning a prospective trial to demonstrate the feasibility, safety and efficacy of WiSE in the LBBAP setting. EBR Systems will support the study financially (scheduled to commence 1H 2022).

[53] Elliott MK et al. 2021. Technical feasibility of leadless left bundle branch area pacing for cardiac resynchronisation: a case series. European Heart Journal – Case Reports. doi.org/10.1092/ehjcr/ytab379.

Benchmarking alternative CSP approaches in a competitive sense. CSP is explored for two reasons: a) as a potential replacement for conventional RV pacing; and b) as an alternative for providing CRT. Both His-bundle pacing (HBP) and left bundle branch area pacing (LBBAP) pacing strategies have support on guidelines as a first line option in patients with conduction blocks (e.g. atrioventricular block or left bundle branch block); or as a rescue strategy for CRT failures (lead failures, non-responders)[54]. HBP is feasible in delivering CRT and may achieve superior electrical synchronisation compared to conventional CRT[55] but it loses capture over time. LBBAP appears to reverse left bundle branch block (LBBB) and deliver CRT more reliably[56]. Results from recent studies is collated in **Table A12** show feasibility. LBBAP is associated with higher success rates but similar outcomes (both symptomatic and structural improvements). Early results are comparable with those reviewed for WiSE. Note that there are no large, well-designed, randomised controlled data for HBP or LBBAP at present.

Table A12. Selected feasibility studies for conduction system pacing

Trial	Design	Indication(s)	n	Success Rate	Outcomes (ECG, QRSd, NYHA)
His Bundle Pacing					
Huang et al. (2019)[57]	Prospective, Observational	LBBB, NYHA II-IV with CRT or pacing indication	74	76%	LVEF 31%→57%; LVESV 140mL→65mL; QRSd 171ms→113ms; NYHA 2.8→1.0
Upadhyay et al. (2019)[58]	Prospective, Rand. crossover	LBBB with CRT indication	41	76%	LVEF 26%→32%; QRSd 172ms→144ms; feasibility as alternative to CRT
Sharma et al. (2018)[59]	Prospective, Observational	CRT indication with BVP failure + primary HBP (LBBB, paced, AVB)	106	90%	LVEF 30%→44% in BVP failures; QRSd 157ms→118ms; NYHA 2.8→1.0; feasibility as alternative to CRT
Left Bundle Branch Pacing					
Vijayaraman et al. (2021)[56]	Retrospective, Observational	CRT indication with LVEF ≤50%	325	85%	LVEF 27%→40% in LVEF <35%; LVESV 171mL→138mL; QRSd 152ms→137ms; NYHA 2.7→1.8; feasibility as alternative to CRT
Wu et al. (2020)[60]	Prospective, HBP v LBBB v BVP; Observational	CRT indication with LVEF ≤ 40% & LBBB	137	100%	ΔLVEF +24%; QRSd 166ms→111ms; NYHA 2.7→1.8; Echo outcomes: LBBB ~ HBP >> BVP.
Huang et al. (2020)[61]	Prospective, Observational	Non-ischaemic LBBB with LVEF ≤ 50%	63	97%	LVEF 33%→55% ; LVESV 123mL→67mL; QRSd 169ms→118ms; NYHA 2.8→1.4; feasibility as alternative to CRT in non-ischaemic pts.
Vijayaraman et al. (2019)[62]	Prospective, Observational	LBBP for bradycardia or CRT with CS lead failure.	100	93%	QRSd 133ms→136ms (162mL→137mL in LBBB subgroup); feasibility as alternative to CRT.

ECG=echocardiography; QRSd=QRS duration; NYHA = New York Heart Association classification; LBBB = left bundle branch block; LVEF=left ventricular ejection fraction; CRT = cardiac resynchronisation therapy; BVP=biventricular pacing; HBP=His bundle pacing; AVB=atrioventricular block; CS=coronary sinus

Source: as referenced, Wilsons

[54] Sharma, P. S. and Vijayaraman, P. (2021) *Condiction system pacing for cardiac resynchronization* Arrhythm Electrophysiol. Rev. 10: 51 – 58.
[55] Arnold, A. D. et al. (2018) *His resynchronisation versus biventricular pacing in patients with heart failure and left bundle branch block* JACC 72: 3112 – 3122.
[56] Vijayaraman, P. et al. (2021) *Left bundle branch area pacing for cardiac resynchronisation therapy: results from the international LBBAP Collaborative Study Group* 7: 135 – 147.
[57] Huang, W. et al. (2019) *Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block.* 105:137–43.
[58] Upadhyay, G. A. et al. (2019) *His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure.* J Am Coll Cardiol 74:157–9.
[59] Sharma, P. S. et al. (2018) His bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: A multicentre experience. Heart Rhythm 15:413–20.
[60] Wu, S. et al. (2021) Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with His bundle pacing and biventricular pacing. Can J Cardiol 37:319–28.
[61] Huang, W. et al. (2020) Cardiac resynchronization therapy in patients with nonischemic cardiomyopathy using left bundle branch pacing. JACC CIin Electrophysiol 6:849–58.
[62] Vijayaraman, P. et al. (2019) Prospective evaluation of feasibility, electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. Heart Rhythm 16:1774–82.

WiSE the only system offering leadless CSP. The *a priori putative* advantages of leadless pacing (low thrombosis and infection risks) apply with equal force in the CSP setting. These clinical factors have been instrumental in the first six years of marketing for Medtronic's Micra in cases of bradycardia-tachycardia and more recently in situations involving atrioventricular block ± atrial fibrillation. Both approved Micra variants pace from traditional lead sites and therefore supply non-physiologic pacing.

WiSE may have procedural advantages over leads in CSP situations. LBBAP is performed with conventional leads (e.g. Medtronic's SelectSecure pacing lead – Model 3830). The electrophysiologist must drive the electrode deep (11-18 mm) into the intraventricular septum from within the right ventricle to reach the left bundle branch which is closer to the LV aspect of the septum. It is not possible to drive a lead electrode from the LV direction because of unacceptable stroke risk. In the recent case series[53] the 3.6mm tines on the WiSE electrode barb allowed sufficient anchoring in the LV septum, deep enough to reach the left bundle system. WiSE is the only system with which leadless conduction system pacing is feasible.

Potential WiSE indications enabled by CSP. We see two important clinical situations where left ventricular septal placement of WiSE may be an attractive option providing LBBAP. What intrigues us about these applications is that they are **not** CRT and therefore bring other patient groups into consideration.

- **Patients with bradycardia secondary to atrioventricular block (AVB).** The AV node is part of the heart's conduction system that electrically connects the atria and ventricles. Patients with an AV block develop abnormally slow heart rhythms (bradycardia). Right-ventricular pacing is the standard of care in these patients but the non-physiological nature of RV pacing is believed to play a role in the development of pacing-induced cardiomyopathy, heart failure and death[63]. This indication would include patients with higher LV ejection fraction and more 'normal' QRS durations with the intention of preventing their deterioration[64].
- **Heart failure patients with permanent or rapidly conducted atrial fibrillation (AF).** CSP's attraction in this setting, again, is that of providing physiological activation and thus preserving the heart's intrinsic ventricular synchrony. Ablating the AV node has been shown to increase the response to CRT. His bundle pacing has had encouraging results in this 'pace and ablate' setting but capture thresholds and lead dislodgement remains a feature. A septal, LV WiSE placement would provide the CSP (via left bundle) whilst leaving the RV pacemaker *in situ* as co-implant signal and back-up RV lead. Many of these patients sit outside the labelled CRT indication (QRS < 120 ms) but could benefit from this form of biventricular pacing support.

[63] Zungsontiporn, N. and Wu, R. (2018) *Can His bundle pacing prevent right ventricular pacing-induced cardiomyopathy, heart failure or death?* J. Thorac. Dis. 10: S3192 – S3194.
[64] Abdelrahman, M. *et al.* (2018) *Clinical outcomes of His bundle pacing compared to right ventricular pacing* JACC 71: 2319 – 2330.

A3.4 Product development opportunities

Our review of WiSE CRT identified several areas for potential development and approval.

A3.4.1 Battery life and transcutaneous charging

EBR is developing a smaller, rechargeable battery system. In the current configuration, battery life is limited to approximately 4.5 years after which it needs surgical replacement. Battery life is a function of how much ultrasound energy is required to capture the electrode. In patients with more distance between transmitter and electrode, battery depletion could occur within a year of implant. EBR's R&D design goal is to develop a battery that can last up to 20 years and is able to be inductively charged through the skin in about one hour each week. Transcutaneous, wireless power transfer is a developing technology but FDA-approved embodiments already exist[65].

A3.4.2 Delivery systems and simulation tools

EBR's current balloon/sheath delivery system is well suited to electrode implantation in the lateral wall of the left ventricle. There may be opportunities to develop new delivery systems for placement in the septum (for LBBAP) which is more challenging. EBR will also continue to produce training and simulation tools. We have received positive feedback in relation to EBR's supporting technology for new physicians which includes a simulation module for electrode placement (Figure A25).

Figure A25. An electrophysiologist practicing WiSE electrode deployment using EBR's simulator on the Mentice platform[67].



Source: EBR Systems

A3.4.3 Electrode retrieval solutions

Device retrieval has been an important design issue in the development of Medtronic and Abbott's leadless pacemakers for the right side of the heart. In the event that the patient's pacing requirements change, it is advantageous to be able to remove the device. Our initial impression is that retrieval is less pressing as an issue for WiSE CRT. CRT candidates are sick patients and unlikely to improve to a point where they no longer require biventricular pacing. Nonetheless, there will likely be situations where the electrode loses capture or individual patient factors impede device performance. The long-term effect of leaving a non-functioning electrode inside the left ventricle is unknown. Another consideration is that of retrieving a device that has come loose from its anchoring point and has embolized within the chamber or elsewhere. We are only aware of two such cases, one of which is reported in the literature[66].

A3.4.4 RV sensing capabilities for de novo conduction system pacing (CSP)

Theoretically, CSP as a pacing strategy has the potential to provide synchronous pacing of the heart via central conduction at a single site, thus obviating the need for stimulating three chambers. Such a device would still require RV sensing capabilities. If the WiSE transmitter could achieve that then no co-implant would be necessary.

[65] Zhou, Y. et al. (2020) *Wireless power transfer for implanted medical application: a review* Energies 13: 2837.
[66] Okabe, T. et al. (2020) *Percutaneous retrieval of an unanchored WiSE CRT system left ventricular receiver electrode* Heart Rhythm Case Reports 6: 579 – 582.
[67] Mentice develops simulation tools for image-guided interventional therapies. See mentice.com

A3.5 Competitive approaches

To the best of our research investigations, WiSE CRT is the only medical device in development for leadless, endocardial pacing in the left ventricle. On that basis, there is a low level of organized competition seeking to extend CRT in the manner that EBR is pursuing. The major CRT companies are taking a different tack: seeking to improve left ventricle lead design to address non-responder and failure rates. Investigator-lead activity is exploring novel pacing strategies using conventional devices.

A3.5.1 Endocardial LV pacing

Around the same time that investigators were implanting patients in EBR's SELECT-LV trial, a competing, investigator-led study was testing the idea of using a Medtronic pacing lead (SelectSecure Model 3830) inside the left ventricle with similar objectives. Investigators on the ALSYNC trial[68] used a steerable guide catheter to introduce the lead via a single pectoral incision to the right atrium, then accessed the left atrium via transseptal puncture. Ultimately the lead was placed inside the left ventricle and fixed to a site on the endocardium. Conscious of thrombosis risk, patients were given intraoperative heparin to avoid coagulation. The safety endpoints included demonstrating ≥70% freedom from complications and recording LV-lead associated adverse events including stroke and death.

Figure A26. Medtronic's SelectSecure Model 3830 pacing lead.



Source: Medtronic

ALSYNC showed endocardial pacing was feasible and salvaged CRT non-responders. The ALSYNC study successfully implanted 118/132 (89%) patients. Among the 14 failed attempts, 11 were delivery system-related, 2 were due to periprocedural atrial clotting and 1 to a perforation. The efficacy signals at 6 months follow up (105/118 pts) showed an encouraging functional result (**Table A13**). Over 40% of the ALSYNC patients were CRT non-responders, but converted to CRT responders with transseptal endocardial LV pacing. 55% of patients had a reduction in LVESV of 15% or more (recall SELECT-LV achieved 52%). Statistically significant changes from base line were also measured for NYHA classification and LV ejection fraction (these results also comparable to SELECT-LV and conventional CRT trials in responder patients).

Table A13. ALSYNC efficacy snapshot

	Baseline	6 months	Δ
n	118	105	
NYHA Class	2.8	2.1	-0.7 (p <0.0001)
I	3%	19%	
II	20%	51%	
III	69%	28%	
IV	7%	2%	
Echocardiographic status			
LVEF (%)	29 ± 10	36 ± 12	7 ± 10 (p<0.0001)
LVESV (mL)	149 ± 79	121 ± 74	29 ± 60 (p<0.0001)

Source: Morgan (2016)[68]

Higher mortality and stroke than that seen with WiSE. ALSYNC patients signed on for life-long anticoagulation therapy as a condition of participation. Five post-procedure strokes were reported (2.6 events per 100 patient-years). Fourteen transient ischemic attacks (9 patients) 5 non-disabling strokes and 23 deaths were reported. Longer term follow-up of the ALSYNC patients showed better responses in lead failure patients than non-responders. The ALSYNC study had significantly higher mortality and cerebrovascular events compared with the WiSE CRT Registry cohort[69].

[68] Morgan, J. M. et al. (2016) *ALternate Site Cardiac ResYNChronization (ALSYNC): a prospective and multicentre study of left ventricular endocardial pacing for cardiac resynchronization therapy* Eur. Heart 14: 2118 – 2127.
[69] Biffi, M. et al. (2018) Benefits of left ventricular endocardial pacing comparing failed implants and prior non-responders to conventional cardiac resynchronization therapy: A subanalysis from the ALSYNC study Int. J. Cardiol. 259: 88 – 93.

A3.5.2 Alternative epicardial strategies and leads

Major CRT manufacturers are focussing on improving the design of their epicardial LV leads to better address the non-responder and lead failure patient cohorts. In the last 10 years, all major manufacturers have released quadripolar LV leads to enhance CRT response rates. These leads offer four pacing locations along the distal end of the lead. Few randomised studies are available investigating the efficacy of quadripolar leads[70]. A recent meta-analysis suggests that quadripolar leads are associated with 43% reduction in the risk of LV lead failure leading to deactivation and a 52% reduction in the risk of lead dislodgement[71].

Table A14. Summary of SOLVE trial outcomes compared with historical outcomes in subjects from comparable CRT studies

Boston Scientific ACUITY X4	Abbott QUARTET	Medtronic ATTAIN (StarFix)
		
Select features include: • Non-apical pacing options • Place more electrodes in mid or basal locations • Dual fixation mechanisms to prevent dislodgment	Select features include: • Claims 97% implant success rates • Improved CRT efficacy and fewer surgical revisions • Multiple shape and electrode spacing options.	Select features include: • Pacing from >1 electrode provides another option for non-responders • Short bipolar options to avoid phrenic nerve stimulation • Active fixation to reduce lead dislodgement (StarFix options).

Source: Boston Scientific, Abbott, Medtronic, Wilsons

A3.5.2 Conduction system pacing

Please refer to Section 3.3.3.

[70] Boriani G,. et *al.* (2016) Cardiac resynchronization therapy with a quadripolar electrode lead decreases complications at 6 months: results of the MORE-CRT randomized trial. JACC Clin. Electrophysiol 2:212–20.
[71] Erath, J. W. et *al.* (2019) Clinical outcomes after implantation of quadripolar compared to bipolar left ventricular leads in patients undergoing cardiac resynchronization therapy: a systematic review andmeta-analysis Europace doi:10/1093/europace/euz196.

A3.6 Reimbursement considerations

Medical device reimbursement is a complex subject and different in every country. This section provides a brief summary of WiSE CRT's currently limited status in a few countries and discusses the likely pathways ahead in major markets. As a general rule, medical devices that attract their own specific forms of reimbursement are favoured by providers. Such favourable coverage is only possible for technologies whose safety, efficacy and health economic benefits are supported by high quality clinical research.

Table A15. Reimbursement status of WiSE CRT

Region	Reimbursement framework
USA	The WiSE CRT procedure is described by eight Category III CPT codes in the USA. Following FDA approval, we would expect EBR to work with professional cardiology and/or electrophysiology societies and the American Medical Association to upgrade these codes to Category I codes. This will allow Medicare to work with physicians and determine an appropriate payment level for each codes. Establishing CPT I codes would allow care settings to bill Medicare and other payers for direct payment covering the cost of the WiSE CRT device.
UK	EBR has established permanent reimbursement in the UK using the High Cost Tariff Excluded Devices Scheme funded by NHS.
European markets	WiSE CRT is covered in Germany under the NUB reimbursement scheme under which select hospitals may bid for a fixed number of paid cases. Similar arrangements operate in the French market under the Forfait Innovation Scheme. Note that these forms of reimbursement are temporary and limited (i.e. France up to ~40 patients covered through scheme only)[72].
Australia	WiSE CRT is not reimbursed currently in Australia.

Source: EBR, Wilsons

A3.3.1 USA

General framework. In the USA we expect that WiSE CRT will be regulated as a Class III medical device, requiring EBR to file a Pre-Market Authorisation (PMA) application with US FDA to gain marketing clearance. In the USA the mechanisms by which hospitals are reimbursed by Medicare and private payers differs on the setting in which those treatments take place for patients. For hospital-based treatment (inpatients), the facility is reimbursed according to Medicare Severity Diagnosis Related Groups (MS-DRGs). In the outpatient setting (Ambulatory Surgical Centres or day hospitals) facilities are paid under Ambulatory Payment Classifications (APCs). DRGs and APCs are similar in that they provide a fixed, predetermined amounts for a procedure, generally covering facilities costs and any medical devices, consumables, radiology or other items used in delivering the procedure. Obviously, facilities are drawn to medical devices that carry their own, specific coverage so that the cost of the device doesn't reduce the profitability of delivering care.

Innovation benefits. Once approved by FDA WiSE CRT becomes immediately eligible for two schemes that may aid market introduction. Both stem from the device's FDA Breakthrough Device Designation (granted in 2019). In inpatient settings (hospitals) WiSE CRT is expected to attract a New Technology Add-On Payment (NTAP) that provides incremental payment to hospitals for 2-3 years in addition to their procedural DRG payment. As discussed in **Section 4** we anticipate that the NTAP component could be >US$20,000. High price is one of the criteria for awarding NTAP (the other two – novelty and clinical benefit) already validated by FDA's Breakthrough decision.

For hospital outpatient procedures, CMS offers Transitional Pass-Through (TPT) status for new product codes that last for three years in addition to the APC payment. Once the NTAP and TPT phases expire, CMS utilises the claims data from WiSE procedures to update DRG and APC payment rates based on standard payment policy.

Coding progress. Currently, there are eight Category III CPT codes that describe the various procedures related to WiSE CRT implantation. If EBR is able to upgrade these to Category I codes they will form a basis for public and private payer billing specific to WiSE.

[72] https://www.prnewswire.com/news-releases/ebr-systems-awarded-prestigious-forfait-innovation-package-for-WiSE CRT-system-by-french-ministry-of-social-affairs-and-health-300888296.htm

Table A16. Category III CPT codes relating to WiSE CRT

CPT Code	Description	Payment
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery]	US$23,040
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only	US$8,152
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; pulse generator component(s) (battery and/or transmitter) only	US$8,152
0518T	Removal of only pulse generator component(s) (battery and/or transmitter) of wireless cardiac stimulator for left ventricular pacing	US$3,440
0519T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter)	US$3,440
0520T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter), including placement of a new electrode	US$23,040
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing	US$24
0522T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, wireless cardiac stimulator for left ventricular pacing	US$37

Source: CMS, Wilsons

Broadly speaking, the US medical device industry considers Medicare as a de facto determiner of coverage policy and price setting. Private, third party payers may or may not follow Medicare's reimbursement practices when considering coverage for non-Medicare beneficiaries (those aged less than 65 years). In line with industry practice, we would expect EBR to set a wholesale price for WiSE CRT close to the available reimbursement thus minimising or even eliminating any out-of-pocket costs to healthcare providers.

A3.3.2 UK

The UK is a single-payer healthcare system where the tax-funded National Health Service (NHS) provides over 75% of all services. Medical device manufacturers are free to set whatever price they choose for products but the NHS often consults the National Institute of Clinical Excellence (NICE) for guidance on cost effectiveness. NICE is yet to consider a formal recommendation for WiSE CRT as a cost-effective intervention for the UK.

A3.3.3 Germany

National coverage by statutory health insurance requires extensive evidence development sometimes conducted within Germany. Reimbursement for outpatient services is based on physician fee schedules, access to which depends on the EBM (einheitlicher Bewertungsmaßstab). Private pay coverage requires similar undertakings through the German Medical Association's Gebührenordnung für Ärzte (GOÄ). Prior to these broad forms of coverage, medical devices can obtain funding under the NUB scheme at select hospitals.

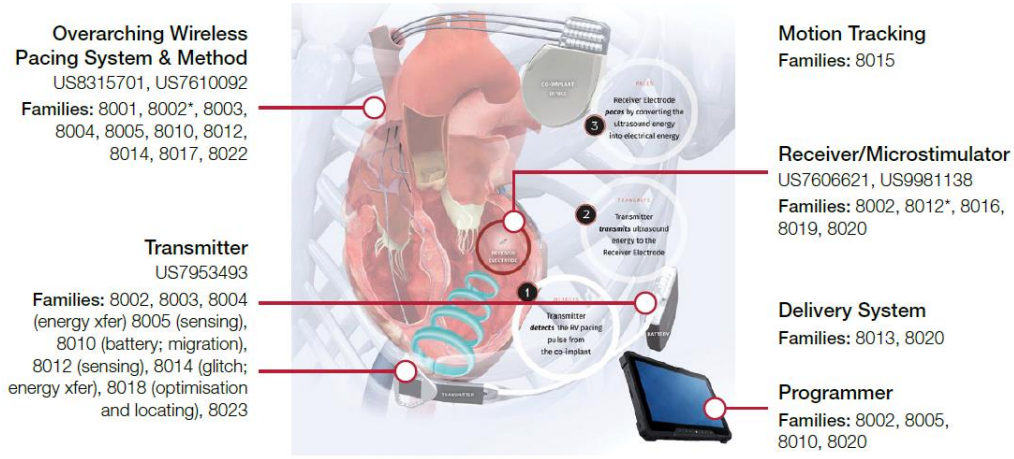
A3.3.4 Australia

In Australia, medical devices must be listed on the Australian Register of Therapeutic Goods (ARTG) to be eligible for any form of reimbursement. Reimbursement is differentiated between those treated under private health insurance and those within the public hospital system under Medicare. Public hospitals are reimbursed for activity under the Australian DRG system. EBR will negotiate WiSE CRT pricing directly with individual hospitals or via state-wide public tenders. For medical devices to be reimbursed within the private system, they must appear on the Prosthesis List. Applications to be included on the Prostheses List are submitted to the Prostheses List Advisory Committee (PLAC) which makes recommendations to the Australian Government Minister for Health as to which products should be covered and at what price.

A4. Intellectual property

The following patent families are owned and/or controlled by EBR Systems. Key patent rights have expiry dates between 2025 and 2029. EBR may be eligible for patent term extensions of up to 5 years in the event of FDA approval.

Figure A27. Overview of patents protecting the WiSE technology



Source: *EBR*

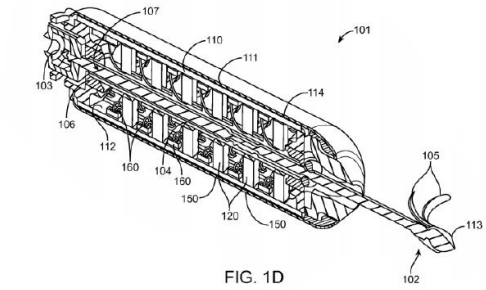
Table A17. Granted patents

Patent family	Granted US Patents	Ownership	Expiry dates	Jurisdictional notes
8001 – Methods and systems for vibrational treatment of cardiac arrythmias.	US 7,006,864 US 7,184,830 US 7,809,438 US 7,050,849	EBR Systems	Jun 2024 Feb 2025 Feb 2025 Jun 2024	Related patents granted in: Germany, Europe, France.
	Summary: These patents are central to the immediate investment case for WiSE, protecting the delivery of controlled vibrational energy, typically ultrasonic energy, to at least a portion of the heart in order to terminate arrhythmias. The ultrasonic energy may be delivered from a distance away from the heart, often from a subcutaneous location immediately outside of the thorax.			
8002 – Leadless cardiac system for pacing and arrhythmia treatment	US 7,610,092 US 7,606,621 US 8,315,701 US 7,996,087 US 7,848,815 US 7,890,173 US 9,008,776 US 7,558,631	EBR Systems	Jun 2027 Mar 2028 Jun 2026 Dec 2025 Dec 2025 Dec 2025 Dec 2025 Jun 2026	Related patents granted in: Europe, Germany, France, UK and Japan.
	Summary: This family of patents claim systems for stimulating cardiac muscle using a subcutaneously implantable controller-transmitter and an implantable receiver-stimulator adapted to contact a cardiac stimulation site. The controller-transmitter is configured to detect a pacing signal from a separate cardiac pacemaker, wherein the controller-transmitter is adapted to transmit acoustic energy upon detecting the pacing signal; and the receiver-stimulator is adapted to receive the acoustic energy and convert the received acoustic energy into cardiac stimulation energy based on both energy and signal information included in the acoustic energy.			

Patent family	Granted US Patents	Ownership	Expiry dates	Jurisdictional notes
8003 – Efficiently delivering acoustic stimulation energy to tissue	US 8,634,908 US 9,014,803 US 9,616,235 US 9,855,429 US 10,576,287	EBR Systems	Sep 2030 Jul 2026 Jul 2026 Jul 2026 Jul 2026	N/A
	Summary: These patents protect the system by which WiSE passes electrical stimulation pulse to cardiac tissue. The system comprises: a controller-transmitter having circuitry which produces an acoustic transmission and includes an energy storage capacitor, wherein the capacitance of the energy storage capacitor is selected to produce the acoustic transmission with an envelope of decreasing amplitude during transmission, and wherein the envelope outlines the peaks of a waveform of the acoustic transmission; and a receiver-stimulator having a circuitry which includes an envelope detector which receives the acoustic transmission and produces an electrical stimulation pulse having a voltage proportional to the amplitude of the acoustic transmission envelope.			
8004 – Methods and apparatus for determining cardiac stimulation sites using hemodynamic data	US 7,702,392	EBR Systems	Oct 2027	Related patents granted in: Germany, Europe, France, UK
	Summary: The method of implanting the WiSE electrode within the heart of a patient, comprising: (a) positioning the stimulation electrode at a test location in the heart of a patient; (b) delivering electrical energy to the location; (c) determining a first acute hemodynamic response in reaction to the electrical energy delivered to the location; (d) assessing whether the first acute hemodynamic response is satisfactory; (e) repeating steps (a) through (d) until the first acute hemodynamic response at the test location is satisfactory.			
8005 – Methods and systems for heart failure prevention and treatments using ultrasound and leadless implantable devices	US 7,765,001 US 9,333,364 US 10,207,115	EBR Systems	Feb 2029 Jul 2027 Aug 2026	N/A
	Summary: Patent claiming the WiSE system specifically for the treatment of heart failure. An acoustic controller-transmitter transmits acoustic energy into a patient's body which provides both energy and signal information to the receiver-stimulator sufficient to stimulate the heart. The receiver electrode generates alternating current to stimulate the cardiac tissue.			
8007 – Acoustically powered wireless defibrillator	US 7,751,881	EBR Systems	Jun 2027	N/A
	Summary: A patent extending WiSE technology to become a leadless alternative to implantable defibrillation (ICD). The subcutaneous transmitter comprises sensing electrodes that detect undesirable cardiac arrhythmias. Acoustic energy is converted to electrical energy by the receiver-defibrillator, stored at a level to produce appropriate amplitude, and then delivered with an appropriate waveform sufficient to treat the cardiac fibrillation or cardiac tachycardia.			
8008 – Systems and methods for implantable stimulation.	US 8,078,283 US 7,899,542 US 7,899,541 US 7,894,907 US 7,894,904 US 7,894,910 US 8,494,642 US 8,494,639 US 8,494,637 US 8,494,643 US 8,498,715 US 9,452,286 US 10,143,850	EBR Systems	Jun 2027	N/A
	Summary: A family of patents protecting the deployment of WiSE technology in stimulating other structures and tissues. The basic format of the invention is consistent: an implanted controller-transmitter to generate acoustic energy, one or more physiological sensors on an external surface of the housing, and an implanted receiver-electrode remotely from the controller-transmitter at a tissue stimulation site. The list of patents encompass: bone, spine, gastrointestinal tissue, nerve, brain, cochlear implants and general tissue stimulation.			

Patent family	Granted US patents	Owner	Expiry date	Jurisdictional notes
8010 – Optimizing size of implantable medical devices by isolating the power source	US 7,953,493	EBR Systems	Jul 2028	Related patents granted in Europe, France, Germany, UK
	Summary: An implantable battery module configured to house a battery to power a transmitter module; wherein the transmitter module is separately implantable and comprises a transmitter enclosure and is configured for transmitting acoustic energy to one or more receiver-stimulator devices implantable in the tissue; wherein the battery module and the transmitter module are connectable by an implantable cable wherein the cable conducts power from the battery to the transmitter module; wherein the cable comprises an antenna, and the antenna is configured to facilitate a low power radiofrequency communication link between at least one of the implantable modules and an external programming module.			
8011 – Local lead to improve energy efficiency of implantable wireless acoustic stimulators	US 9,731,139	EBR Systems	Jul 2028	N/A
	Summary: A method of optimizing the placement of transmitter and implanted electrode within acoustic window constraints. A local lead is deployed at a second cardiac tissue location to minimize the distance and angle of the acoustic energy transmission from the transmitter to the primary receiver.			
8012 – Operation and estimation of output voltage of wireless stimulators	US 8,364,276 US 9,981,138 US 8,588,926 US 9,180,285 US 9,343,654 US 10,052,493 US 10,806,938 US 10,512,785	EBR Systems	Apr 2030 May 2029 Mar 2029 Mar 2029 Mar 2029 Mar 2029 Mar 2029 Mar 2029	Related patents granted in Germany, Europe, France, UK
	Summary: The IP surrounding the implantable receiver-electrode component of the WiSE system. The electrode harvests acoustic power from an acoustic field and generates electrical power. The device comprises a sealed enclosure, housing acoustic piezoelectric components which convert the acoustic field to electrical power. Stimulation electrodes deliver output to tissue at sufficient electrical energy levels to stimulate contraction.			
8013 – Temporary electrode connection for wireless pacing systems	US 9,283,392 US 9,907,968 US 10,688,307	EBR Systems	May 2029 Mar 2029 Mar 2029	Related patents granted in Europe, France, UK, Germany
	Summary: This aspect of the IP be releasably connected to a delivery system to attach the receiver-stimulator to the heart of a patient, wherein the receiver-stimulator is configured to receive acoustic energy from a controller-transmitter and to convert the acoustic energy to electrical energy, wherein the receiver-stimulator includes a first electrode, a second electrode, and an electrical contact electrically connected to the first electrode, wherein the first and second electrodes are configured to deliver the electrical energy to the heart, and wherein the electrical contact is electrically connected to the delivery system when the receiver-stimulator is connected to the delivery system; and a disconnect mechanism including a seal configured to electrically insulate the electrical contact from the patient to block a current path through the patient between the electrical contact and the second electrode when the receiver-stimulator is released from the delivery system.			
8014 – Systems, devices and methods for selectively locating implantable devices	US 9,616,237	EBR Systems	Sep 2033	N/A
	Summary: Specific patent protecting the way WiSE works with the signal from a co-implant to provide biventricular pacing. The implanted electrode comprises a glitch generator that modifies its electrical output at a pre-configured interval, based on pacing information from the co-implanted pacemaker/ICD/CRT device.			

Figure A28. Internal structure of the WiSE electrode features an array of piezoelectric components that convert ultrasound energy to electrical energy for tissue stimulation.



Source: US 9,343,654

Patent family	Granted US patents	Owner	Expiry date	Jurisdictional notes
8018 – Optimizing energy transmission in a leadless tissue stimulation system	US 8,718,773	EBR Systems	Jun 2030	Related patents granted in: Japan, UK, France, Europe and Germany
	US 10,080,903		May 2027	
	US 10,456,588		May 2027	
	A system for locating an acoustic receiver-stimulator, comprising: an implantable acoustic controller-transmitter comprising an array of acoustic transducers configured to transmit focused acoustic energy to a tissue location; at least one implantable acoustic receiver-stimulator adapted to receive the focused acoustic energy and convert the focused acoustic energy into electrical energy; wherein the receiver-stimulator further comprises two electrodes configured to be in electrical connection with tissue and to deliver the electrical energy to the tissue; wherein the controller-transmitter is configured to detect the delivered electrical energy to determine whether the receiver-stimulator is present at the tissue location; and wherein the controller-transmitter is further configured to adjust the transducer array to transmit focused acoustic energy to the tissue location associated with the detected electrical energy.			

Source: EBR, USPTO, Wilsons

Table A18. Patent applications

Patent family	US application	Owner	Expiry date	Jurisdictional notes
8015 – Systems, devices and methods for electromechanical sensing and mapping	16/637,130	EBR Systems	Aug 2038‡	Pending application in Europe.
	Summary: Enhanced IP protecting the way that the implantable acoustic transmitter (and its transducers) are configured to transmit ultrasound to a cardiac tissue. The movement of the implanted electrode is tracked by measuring the delivered electrical energy to create a motion profile relative to the tissue.			
8016 – Pulse delivery device including slew rate detector and associated systems and methods	16/557,367	EBR Systems	Aug 2039‡	Pending application in Europe.
	Summary: Enhanced IP regulating the output voltage from the implanted electrode. The circuit includes a switch and a slew rate detector configured to detect whether a voltage rate of an individual pulse of the input voltage signals exceeds a predetermined threshold rate, wherein the circuit is configured to change the switch from the closed state to the open state in response.			
8017 – Devices, systems and methods for cardiac resynchronisation therapy	16/773,599	EBR Systems	Jan 2040‡	Pending applications in Europe and Australia.
	Summary: Specific protection for WiSE CRT in the treatment of patients with left bundle branch block (LBBB).			
8018 – Optimizing energy transmission in a leadless tissue stimulation system	16/601,854	EBR Systems	Oct 2039‡	Related patents granted in: Japan, UK, France, Europe and Germany
	Summary: This patent application aims to protect an aspect of the subcutaneous transmitter assembly. An acoustic signal is emitted to locate the receiver electrode in the left ventricle. This enables the transmitter to target and optimise the wireless transfer of ultrasound energy to the electrode.			
8019 – Endocardial pacing electrodes with tissue engagement mechanisms	17/402,252	EBR Systems	Aug-2041‡	PCT filing
	Summary: This patent application is unpublished.			
8020 – Systems and methods for endocardial contact sensing with a sheath balloon for wireless endocardial pacing electrodes	17/404,502	EBR Systems	Aug-2041‡	PCT filing
	Summary: This patent application is unpublished.			
8022 – Systems and methods for wireless endocardial stimulation of the left ventricular septal wall	63/111,512	EBR Systems	Nov-2040‡	PCT publication pending.
	Summary: This patent application is unpublished.			
8023 – Cardiac pacing transmitter systems with rechargeable potteries and associated devices and methods	63/111,540	EBR Systems	Nov-2040‡	PCT publication pending.
	Summary: This patent application is unpublished.			

‡ assumes patent term of 20 years from US filing date.
Source: EBR, USPTO, Wilsons

A5. Board & Management

A5.1 Board

Allan Will – Executive Chairman

Mr Will served as the CEO of the Company from 2011 until 2019, and has served in the role of Executive Chair since 2019. Previously, as chair of Ardian, Inc., Mr Will led negotiations of the company's acquisition by Medtronic Inc. for over US$800 million. Mr Will was also founding Managing Director of Split Rock Partners' Silicon Valley office, focusing on therapeutic medical devices. Mr Will was founder, chair and CEO of The Foundry, co-founding 11 companies there, including Ardian, Evalve, Inc. (acquired by Abbott Laboratories for US$450 million) and Concentric Medical Inc (acquired by Stryker Corp for US$135 million).

John McCutcheon – Managing Director

Mr McCutcheon has served as President and CEO of EBR since June 2019 and is responsible for the overall management and strategic direction of EBR. Mr McCutcheon has over 35 years' experience in sales, marketing, and management of medical device companies. Prior to joining EBR, Mr McCutcheon was the President and CEO of Ceterix Orthopaedics, Inc. for nine years from 2010 to 2019. He also held CEO roles at Ventus Medical, Inc. (2009-2010) and Emphasys Medical, Inc. (2000-2009).

Dr Chris Nave – Non-executive Director

Dr Nave is a founder and Managing Director of Brandon Capital Partners and the CEO of the Medical Research Commercialisation Fund. Dr Nave previously served as the Director of Commercialisation at the Baker Heart Research Institute. Dr Nave is currently a director of The Australian Investment Council, Azura Ophthalmics, Inc., Certa Therapeutics Pty Ltd, Global Kinetics Corporation Ltd, OccuRx Pty. Ltd., Osprey Medical, Inc. (ASX:OSP), PolyActiva Pty Ltd and Que Oncology, Inc. Dr Nave was chairperson of Fibrotech Therapeutics Pty Ltd at the time of its successful sale to Shire Plc and a director of Spinifex Pharmaceuticals, Inc. at the time of its sale to Novartis International AG.

Trevor Moody – Non-executive Director

Mr Moody currently serves as Medical Device Partner at M.H. Carnegie & Co (since October 2013), where he makes investments in medical device companies. Mr Moody was previously a General Partner at Frazier Healthcare Ventures, a large U.S. based private equity and venture capital firm. Mr Moody is currently a director of electroCore, Inc. (NASDAQ: ECOR), Australian Medtech Services Pty Ltd, Cardiac Dimensions Pty Ltd, Renew Medical Pty Ltd, Serene Medical Pty Limited, The Brain Protection Company Pty Ltd, and CurvaFix, Inc.

Dr Bronwyn Evans – Non-executive Director

Dr Evans AM is an experienced leader and CEO with a broad technical background across multiple industry sectors including medical technology, manufacturing, power generation and distribution and technical regulation and standards. Dr Evans is currently the CEO of Engineers Australia, the Chair of Building 4.0 CRC, and the Director at GME Pty Ltd. Prior to her role with Engineers Australia, Dr Evans held various senior engineering roles, including at Cochlear and GE Healthcare.

Dr David Steinhaus – Non-executive Director

Dr Steinhaus retired in 2019 as Vice President and General Manager of the Heart Failure Business for the Cardiac Rhythm and Heart Failure Division at Medtronic plc (NYSE:MDT). Dr Steinhaus joined Medtronic in 2005, after 20 years of cardiology (electrophysiology) practice. Dr Steinhaus' responsibilities at Medtronic included bringing the physician voice to CRHF, identifying future opportunities in new product development. Dr Steinhaus has been closely associated with research and academia, performing extensive clinical studies in implantable cardiac devices and leads.

Karen Drexler – Non-executive Director

Ms Drexler is a serial entrepreneur with expertise in the fields of digital health, medical devices, and diagnostics. Ms Drexler serves on the boards of two other public companies, Resmed, Inc. (NYSE, ASX:RMD), where she serves on the compensation and nominating and governance committees, and Outset Medical Inc.(NASDAQ: OM), where she chairs the compensation committee and serves on the nominating and governance committee. Ms Drexler is also on the board of three private companies: Bone Health Technologies Inc., a medtech company focused on treating osteoporosis and its precursor, osteopenia, VIDA Diagnostics Inc., an artificial intelligence powered lung imaging solutions company, and Tivic Health Systems, Inc., a bioelectric medicine company focused on relief of congestion and sinus pain.

A5.2 Management

John McCutcheon – Chief Executive Officer

As above.

Frank Hettmann – Chief Financial Officer

Mr Hettmann joined EBR as CFO in May 2021. Mr Hettmann has over 25 years of experience in senior and executive positions in finance, operations and administration within medical device and technology companies. Prior to joining EBR, Mr Hettmann was the CFO of Avenu Medical, Inc. (acquired by Medtronic). He also previously served as CFO of Neology, Inc. and has held other executive-level finance positions at both publicly-traded and venture-backed companies in the U.S.

Dr Parker Willis – Chief Technology Officer

Dr Willis has served as CTO at EBR since September 2011 and previously served as Vice President of Research since 2006. Dr Willis is an electrical engineer and has worked in medical devices for over 25 years, all in technical leadership capacities for development of novel technologies for cardiac electrophysiology. He previously held senior positions at Boston Scientific Corporation (NYSE: BSX) and Cardiac Pathways Corporation.

Michael Hendrickson – Chief Operating Officer

Mr Hendrickson joined EBR with over 25 years of medical device product development and manufacturing experience. Michael was COO at Ceterix Orthopaedics (Ceterix) where he led the development of the NOVOSTITCH Pro Meniscal Repair System. Ceterix was acquired in 2019 by Smith & Nephew. Prior to Ceterix, Michael was Vice President of R&D at Foundry NewCo XI and has also served in engineering roles at multiple medical technology companies.

Steve Sandweg – Chief Commercial Officer

Mr Sandweg is responsible for all commercialisation activities, including global field operations, SOLVE-CRT clinical trial enrolment, marketing, and preparation activities for commercial launch. Steve has 30 years of sales experience in Fortune 500 medical technology companies, primarily within the cardiovascular and structural heart space. Most recently, Steve served as General Manager for Keystone Heart, a Venus Medtech Company, where he was responsible for all clinical, commercial, quality, regulatory and compliance activities within the US and Europe. He also previously led several strategic product launches at Medtronic, including Medtronic's first drug-eluting stents, Endeavour and Resolute, and Medtronic's first transcatheter aortic valve devices, CoreValve and EVOLUT.

Dr Spencer Kubo – Chief Medical Officer

Dr Kubo has served as CMO at EBR on a contract basis since November 2018. Dr Kubo has extensive experience developing innovative cardiovascular devices including neuromodulation, mitral regurgitation and cardiac support. Dr Kubo holds an MD degree and is a Fellow of the American College of Cardiology.

Madhuri Bhat – Chief Regulatory Officer

Ms Bhat has over 20 years of experience in public affairs, public policy, clinical, quality assurance, and regulatory roles in medical devices. She has led several successful pivotal clinical trials, registries and secured regulatory approvals and clearances in the U.S. and internationally for Class II & III cardiovascular systems. Ms Bhat holds a B.S. from the University of Bombay and a Master of Public Policy from Duke University.

Andrew Shute – SVP Global Field Operations

Mr Shute has over 20 years of medical device experience and has led the successful commercialisation of new technologies and products working in corporate start-up and distributor settings. Mr Shute holds a BSc from the University of Wollongong.

John Sam – VP Engineering and Operations

Mr Sam has over 15 years of medical device experience and has managed, supported and transferred many different technologies and products from concept to commercialisation. Mr Sam holds a B.Sc.in Mechanical Engineering from California Polytechnic State University and a Master of Engineering Management from Santa Clara University.

EBR Systems Inc. (EBR)

Business description

EBR Systems develops, manufacturers and markets medical devices for cardiac rhythm management.

pioneered the development of 'leadless pacing' for the left side of the heart. They did it because nearly a third of patients who qualify for cardiac resynchronisation therapy (CRT) either cannot be implanted with leads or whose leads fail to provide a benefit. The major rhythm management companies (Medtronic, Abbott, Boston Scientific) either couldn't do it (technologically challenging and associated with high clotting risks) or were not interested in doing it (believing that better lead design would solve the problems posed by leads). EBR implanted their first human patient in 2011, concluded a compelling feasibility study in 2016 and next year will report results from a pivotal, PMA-enabling trial

Investment thesis

We initiate coverage of EBR Systems at an OVERWEIGHT rating with a $1.50 12-month PT. EBR is a medical device developer pioneering ways to pace the left side of the heart without using wire leads. EBR's work immediately extends the rhythm management market by offering a solution for the 30% of patients who are untreated. In the background, a second and potentially more powerful structural thematic is building. All global rhythm management peers are developing 'leadless pacing' for the right side of the heart but ignoring the left. They are creating a growing pool of leadless recipients who will ultimately need pacing on the left side of their hearts as well (most notably, those who develop heart failure). EBR's WiSE is the only technology that can 'upgrade' those patients without leads. We assess a US$1.06B TAM developing by 2025 in EBR's initial markets. Investigator-led research is taking WiSE into new indications including conduction system pacing. There are significant opportunities for indication expansion into de novo implants and difficult to treat populations with electrically blocked hearts and/or atrial fibrillation.

Revenue drivers

- Major market regulatory approvals and jurisdictional product launches.
- Off-label use and indication expansion.
- Market penetration.

Balance sheet

- Forecasting net cash of US$82M as at the end of 2021.

Margin drivers

- Strong ASP during market introduction phase in the USA.
- Forecast gross margin improvement >70% at scale.
- Operating expense discipline with respect to R&D and SG&A.

Board

- Allan Will – Executive Chairman
- John McCutcheon – Managing Director
- Dr Chris Nave – Director
- Trevor Moody – Director
- Dr Bronwyn Evans – Director
- Dr David Steinhaus – Director
- Karen Drexler - Director

Key issues/catalysts

- Positive clinical trial results including SOLVE-CRT pivotal study.
- Major market authorizations.
- Real word evidence development promoting clinical adoption.
- Development of the leadless pacemaker recipient population as pool of likely WiSE CRT recipients.
- Patent term extensions.

Management

- John McCutcheon – CEO
- Frank Hettman – CFO
- Dr Parker Willis – CTO
- Dr Spencer Kubo – CMO
- Andrew Shute – SVP Global Field Operations
- Madhuri Bhat – SVP Regulatory Affairs & QA
- John Sam – VP Engineering and Operations

Risk to view

- Equivocal or adverse clinical trial outcomes.
- Regulatory set-backs.
- Execution risk relating to product roll-out.
- Manufacturing, quality and product safety including the risk of product recalls or other voluntary field actions.
- Intellectual property and competitive risks.
- Potential requirement for further equity capital.

Contact details

EBR Systems
480 Oakmead Pkway
Sunnyvale CA 94085
USA

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Recommendation structure and other definitions

Definitions at wilsonsadvisory.com.au/disclosures.

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Wilsons contact

For more information please phone: 1300 655 015 or email: publications@wilsonsadvisory.com.au