A PROSPECTIVE MULTI-CENTRE STUDY OF EFFECTIVENESS OF RIPPLE MAPPING FOR ATRIAL TACHYCARDIA ABLATION

Ripple AT

JRCO and insurance reference: 14HH2319

Protocol - Version 1.1 (13th February 2015)

Study Sponsor: Imperial College Healthcare NHS Trust

STUDY COORDINATION CENTRE: Hammersmith Hospital Campus, Imperial College Healthcare, London

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This protocol describes the Ripple AT study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections and amendments may be necessary. These will be circulated to the investigators in the study. Problems relating to this study should be referred, in the first instance to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd Edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

3D	:	3-Dimensional
AE	:	Adverse Event
bpm	:	Beats per minute
DSMB	:	Data & Safety Monitoring Board
eCRF	:	Electronic Case Report Form
ECG	:	Electrocardiogram
GCP	:	Good Clinical Practice
ICTU	:	Imperial College Trials Unit
LA	:	Left Atrium
ms	:	Milliseconds
mV	:	Millivolts
NA	:	Not applicable
NHS	:	National Health Service
R&D	:	Research and Development
SAE	:	Serious Adverse Event
sec	:	Seconds
SSA	:	Site Specific Assessment
SVT	:	Supraventricular tachycardia
UADE	:	Unanticipated Adverse Device Effect
W	:	Watts
RM	:	Ripple Mapping
AT	:	Atrial tachycardia

Ripple - AT Protocol Summary

SPONSOR	Imperial College Healthcare NHS Trust
PROTOCOL TITLE	A PROSPECTIVE MULTI-CENTRE STUDY OF EFFECTIVENESS OF RIPPLE MAPPING FOR ATRIAL TACHYCARDIA ABLATION
STUDY HYPOTHESIS	Ripple Mapping is superior to isochronal activation mapping in diagnosing the mechanism of atrial tachycardia and guiding the delivery of radiofrequency ablation.
STUDY DESIGN	Multicentre, prospective randomised clinical trial
TREATMENT REGIMEN	Randomisation to Ripple Mapping guided AT ablation vs. conventional AT ablation.
INCLUSION CRITERIA	1. Patients undergoing clinically indicated ablation of sustained atrial tachycardia (post AF ablation) using 3D mapping. 2. Signed informed consent
EXCLUSION CRITERIA	1. Patients with typical flutter. 2. Patient with non-sustained atrial tachycardia 3. Contraindication to catheter ablation 4. Unable to give informed consent
NUMBER OF PATIENTS	~100 patients, 1:1 randomisation
NUMBER OF SITES:	7
Site Selection Criteria	To perform 4-5 consecutive Ripple mapping guided AT ablations.
PRIMARY ENDPOINT	1) Tachycardia change/termination with first ablation set after map categorisation.
SECONDARY ENDPOINT	1) Tachycardia change/termination during point collection 2) Tachycardia change/termination during pacing manuoevre 3) Failure to ablate/ change tachycardia with ablation. 4) The need for entrainment mapping

1.1 INTRODUCTION

The difficulties of using electroanatomical mapping systems in the diagnosis and treatment of atrial tachycardias are widely recognised and result from several factors, including inappropriate setting of the "window of interest" in relation to a reference time point, mis-annotation of signals within that window and misinterpretation of the resultant color-coded map. Ripple Mapping (RM) as a novel 3D mapping system that has the advantage of not needing to set a "window of interest", avoids interpolation between points and minimises user post-processing (Linton et al. 2009).

The RM system has been described in detail previously and displays each electrogram at its corresponding 3D coordinate on the surface of the cardiac chamber as a dynamic bar that changes in length according to the electrogram voltage–time relationship (Linton et al. 2009). Each point is time-gated to a selected fiduciary reference electrogram and can be superimposed on a surface bipolar voltage map identifying any scar. Importantly RM does not need LAT annotation as direction of activation is visualised by the relative motion of each ripple bar.

An off-line prototype RM system incorporated with CARTO-XP™ was validated using atrial tachycardia and demonstrated that experienced CARTO users had improved diagnostic yield using RM for the first time compared to standard CARTO activation maps (80% vs 50%) without any other EP data (Jamil-Copley et al. 2013).

The residual error rate of 20% in the RM group was higher than expected. This was thought to be related to several standard CARTO based approaches to data collection and interpretation being inadequate for RM (Koa Wing 2014). These included:

1. Insufficient or unevenly distributed points, leaving areas without activation data.
2. Parts of the activation map not being 'seen' due to <100% of cycle length collected.
3. RMs played using the default bar and scar settings

A standardized diagnostic algorithm to data collection and RM interpretation was developed with the aim of minimizing errors and improving diagnostic accuracy (Koa Wing 2014). Ripple Mapping is now incorporated in CARTO3 v4, and this algorithm can now be tested prospectively.

The AT substrate can demonstrate widespread area of scar around which the wavefront propagates. Using Ripple mapping to combine both voltage and activation data during tachycardia identifies isthmuses of tissue (with Ripple bars propagating across) bordered by areas of functionally inactive tissue (with no Ripple activity) which may be critical for the tachycardia circuit. In patients with complex atrial substrates, ablation of these isthmuses

identified using Ripple mapping may lead to tachycardia termination in otherwise unsuccessful cases.

This study is based on the following observations;
i) Activation mapping requires accurate assignment of local activation times.
ii) Activation mapping is dependent on an appropriately set window of interest (WOI)
iii) It is not known how often these potential sources of error lead to operators relying on additional pacing manuoevres to make a diagnosis
iv) It is not known how often ablation is delivered after an inaccurate diagnosis
v) Conventional mapping leads to difficulties in defining scar.
v) Ripple mapping is not susceptible to annotation or WOI errors, but operators have to interpret moving wavefront.

1.2 HYPOTHESIS

Ripple Mapping is superior to activation mapping in diagnosing the mechanism of atrial tachycardia and guiding the delivery of radiofrequency ablation.

1.3 OBJECTIVE

To compare the effectiveness of Ripple Mapping against conventional activational mapping as determined by:

1. The operator's confidence in the diagnosis of the mechanism of atrial tachycardia from their first map collected.
2. The percentage of cases where the tachycardia changes/terminates with first ablation set after map categorisation.
3. The amount of ablation required; the overall procedural time; dependence on entrainment mapping to make diagnosis.

2. STUDY DESIGN

This is a multi-centre prospective open randomised control study of 100pts comparing RM guided AT ablation against conventional AT ablation.

2.1 SITE SELECTION CRITERIA

Centres and investigators will undertake a minimum of 4-5 consecutive Ripple mapping guided AT ablations prior to starting the randomized study. These cases will be reviewed with the Trial Management team.

2.2 RANDOMISATION

Patients referred for clinically indicated AT ablation by their electrophysiologist will be recruited. For each patient recruited to the study, they will be block randomized into 2 arms - Ripple Mapping guided ablation, or conventional ablation.

2.3 MAPPING PROTOCOL

2.3.1 Generalized approach

Patients will be studied in the post-absorptive state. Trans-oesphageal echo will be used to exclude LA thrombus as per local protocol. Periprocedural anticoagulation will be as per local protocol. Patients will be prepared for AT ablation as per local protocol which may include sedation/GA, pressure sensing catheter and deflectable sheaths but must use the CARTO 3 Version 4 system for mapping. Each centre can use their preferred radiofrequency ablation catheter approach and settings, but this must be same for both groups. A detailed CARTO-3v4™ (Biosense Webster, USA) electroanatomical map will be collected using a 3.5-mm Navistar Thermocool catheter or LASSO Nav (Biosense, Inc.).

A decapolar catheter will be placed in the coronary sinus and a suitable CS reference is selected. The operator may set a window-of-interest suitable for isochronal activation mapping if required.

2.3.2 GROUP 1 (RIPPLE MAPPING)

If the CS activation is proximal-distal and the surface ECG is inconsistent with CTI dependent flutter, a right atrial map should be generated first. The map should be collected as a bipolar voltage map with "Scar auto tagging" turned off. The isochronal activation map must not be seen by the operator.

2.3.2.1 Collecting Data for Ripple Mapping

Ripple Mapping is most effective with raw data collected evenly throughout the whole chamber-of-interest so that activation can be visualised globally during the whole cycle length. The introduction of multipolar mapping and the ability to acquire several hundred points within a short period of time has facilitated the process of creating a high density map. Importantly, in post-AF ablation tachycardias where the substrate is complex, it is important to understand activation patterns within scarred region. Most operators will not usually collect a high density of points within scar as these are difficult to annotate but with Ripple Mapping this is no longer an issue and important mechanistic data is revealed by ensuring dense scar collection.

Attention should be made to ensure structures such as valve annuli and pulmonary vein ostia are mapped adequately and once the map has been collected, the valve annuli should be cut out.

2.3.2.1.1 Map Setup and Map Collection: Fast Anatomical Maps in Stable mode are selected on the Map Setup screen. Do not opt to "apply the FAM to collected points" in order to create a smooth contoured shell. Having "Initialized", limit the mapping resolution to 10 to

ensure a smooth surface. The map is collected as a bipolar voltage map. "Scar auto tagging" is turned off, in order to map the entire chamber evenly throughout, and importantly this includes all scar. Set the fill and colour threshold to 5mm to see areas without point acquisition and to help fill in all the areas. Collect at least 250 points, ensuring >25 points around anatomical structures e.g. valve annulus, pulmonary veins so the activation direction can be clearly seen. Annular signals are tagged separately on the map and the valve annulus is removed.

2.3.2.1.2 ConfiDENSE: An alternative to point-by-point collection is the use of the CARTO3 v4 ConfiDENSE Continuous Map Acquisition function. High point density acquisition improves RM interpretation and we have been able to collect substantially higher number of points (>2000 points in approximately 15 minutes with a LASSO NAV) using this facility. A series of point filters are available as shown in the image below;

The following are optimal for Ripple mapping;

Cycle Length (CL) Range: ±5% of the TCL
A point will only be collected if the cycle length is within this defined range. This avoids ectopic beats and major cycle length variation causing problems in interpretation. Such points are easily seen as rogue points in a Ripple Map but obviously it would be better not to collect these in first place.

Position Stability: 2mm (range is 0-12mm)
Ensuring the catheter is stable before collecting the point is considered to reduce noise signal from catheter movement.

Density: 3mm (range is 1-4mm)
A 3mm inter-point distance is the ideal balance between a dense map and one that results in overcrowding of Ripple bars.

LAT stability: switched OFF.
As Ripple Mapping is not dependent on LAT annotation, application of this filter may slow down map acquisition collection. This is an important function when using an activation map with Continuous Acquisition but not necessary for Ripple Mapping.

2.3.2.1.3 Which chamber to map first? If coronary sinus activation is "proximal to distal" and isthmus dependent right atrial flutter cannot be excluded on 12 lead ECG, in order to avoid tachycardia change or termination with entrainment, a right atrial map should be collected first.

2.3.2.2 The CARTO Ripple Map user interface

There are three toolboxes relating to Ripple Mapping in the CARTO 3 v4 User Interface. These are called “Ripple Map Preferences”, the “Ripple Cine Player”, and the “Ripple Viewer” and are described in detail below.

2.3.2.2.1 Ripple Map Preferences (Tools > Ripple Map Preferences): This provides a series of options that determines the voltage at which bars are visible and the voltage-height relationship.

‘Show bars above’ dialog box is used to enter the minimum voltage at which the Ripple bars become visible. As every deflection within the electrogram is shown by the moving bar on the map, it is helpful to remove noise from the signal. ‘0.03mV’ (default) is a reasonable setting to eliminate noise artefact for SmartTouch catheters and ‘0.07mV’ for LassoNav catheters. Obviously, for every Lab this may be different and it is important to reduce noise as much as possible and have this setting as low as possible. This will enable the lowest amplitude signal to be seen on the Ripple Map.

‘Size factor’ collectively magnifies or reduces the height of the bars. Options include x1, x2, x4, x8. The default setting is X8.

‘Clip bars above’ option will limit the height of the bar at the level which represents that voltage. For example, if bars are clipped above 0.5mV and the electrogram reaches 5mV at its peak deflection, then it will remain at the height attained for 0.5mV until the voltage falls below this level. If the bars are too small, it can limit visualisation of the Ripple wavefront. However, if the bars are too tall, they can overcrowd the atrial geometry and overlap each other again making interpretation difficult. In most cases, the isthmuses of interest will have low amplitude signal and may lie within or near regions of scar, so the bars will be set up to optimise for these low amplitude signals with bars shown above 0.03mV and clipped at 0.25mV with Size set to High. The User can adjust these three parameters to maximise the effectiveness of visualisation in other situations.

‘Show markers’ option on the “Ripple Map Preferences” screen does not relate to the bar height settings. Selecting this option allows “Ripple Markings” to be visualised on the map. “Ripple Markings” are discussed in detail below (see Ripple Viewer section).

2.3.2.2.2 Ripple Cine Player (Map>Ripple Map>Play): This is used to view the Ripple Map. The playback speed can be selected by the operator and options are: x1, X2 , X3, x4, x5. Default is x4.

When played, the Ripple Map automatically runs in a continuous loop. Playing the map using the default settings enables a rapid appreciation of the global activation pattern. At

areas of interest, the playback speed can be reduced to study local electrograms and patterns of activation. Of note, the map can be played frame by frame, including in reverse, which is particularly useful when trying to find the earliest bar during focal activation.

2.3.2.2.3 Ripple Viewer (Window > Ripple Viewer): This function allows the user to define the duration of the 'time-window' viewed as a Ripple map. It also enables the operator to review a series of electrogram signals from an area of interest with marked points (mouse right click > Ripple Markings) side by side. This can be used to observe local activation sequences along potential conduction channels or electrogram morphology. For example, it is particularly useful to determine if the complete cycle length has been mapped in a circuit or which limb of a dual-loop circuit enters the common isthmus first. These "Ripple markings" can be hidden from the map by unselecting the "show markers" option on the Ripple "Map Preferences" panel

2.3.2.3 Analysing a Ripple Map

A Ripple Map will show more information than current mapping systems and it is helpful to go through a set approach to familiarise the operator.

2.3.2.3.1 Set up Ripple Viewer to display multiples of full tachycardia cycle length: The Ripple Viewer is used to define the duration of the 'time-window' presented as a Ripple map. When first displayed, the timings are automatically set to the LAT Window of Interest around the reference signal (red dotted line) as defined by the operator at the beginning of the case. Lead II body surface channel is always displayed in the viewer. Displaying two complete cycle lengths of the tachycardia in the Ripple Viewer guarantees the whole circuit is viewed without interruption. The Ripple Viewer calipers can be manually set to display 2 full tachycardia cycle lengths.

2.3.2.3.2 Set up Ripple Preferences and Ripple Cine Player: Once the Ripple Map is playing, the user will be able to identify wavefronts moving around the chamber. In cases of focal tachycardia the mechanism may be obvious at this stage.

2.3.2.3.3 Dynamic Scar Thresholding: Ripple Map displays both voltage and activation information on the same map. Dynamic scar thresholding is a process of altering the scar bipolar voltage settings to display only areas dense scar without a propagating wavefront. As there is no nominal scar setting for atrial voltage maps, an arbitrary high empirical scar setting should be applied. As scar settings are reduced, potential isthmuses of conduction may be seen, bounded by either areas of scar, anatomical boundaries (veins, valve annuli) or previous ablation lines. A narrow window between the upper and lower voltage (eg. 1mV-1mV) is applied as this presents a clear distinction between areas depicted as healthy (purple) and scar (red). With a large difference (eg 1mV-0.8mV) additional colors are seen on the voltage map (yellows, greens, blues etc) which can be a distraction. Maps should be

collected as a bipolar voltage map using empirical scar setting of 1mV-1mV. Having appreciated global activation, the scar settings should be reduced in a stepwise fashion (e.g. 0.5mV-0.5mV, 0.4mV-0.4mV, 0.3mV-0.3mV, 0.2mV-0.2mV, 0.1mV-0.1mV) until only areas marked as scar (red in color) are those that lack clear Ripple wavefront propagation. This has often highlighted islands of scar bordering isthmuses of conducting tissue.

2.3.2.3.4 Review Chamber in multiple orientations. The first moment the Ripple map is played, in particular with very high point density (>1000 points), there can be so much information displayed on the map that a systematic approach is helpful. First begin by localising an obvious area of Ripple wavefront on the map. Next, rather than following the wavefront in the direction of activation, rotate the map in the opposite direction. Progressively following the wavefront in reverse can be a useful way of tracking the origin of activation in a focal tachycardia or completely around the map in a macroreentrant circuit.
At areas of interest, the playback speed can be reduced (60fps or 20fps) to study local electrograms and patterns of activation.

If a focal tachycardia is suspected, the times frame in the Ripple Viewer can be shortened to remove electrical inactivity in order address the area of electrical breakout. The map can be played frame by frame using the Step forward/back icon in order to identify the earliest Ripple Bar representing the focal origin. In most cases focal tachycardias are relatively easy to identify so long as activation is seen to travel in all directions from the source. If the source is at an anatomical edge such as the annulus or the scar then the operator needs to be aware that if the anatomical boundary or scar has not been fully mapped then errors can occur.

Macroreentrant circuits can be more complicated. The left anterior oblique view with the valve en-face should be used to exclude peri-annular dependent circuits, and right lateral view to check for roof dependency. Following this each view is reviewed to understand further aspects of the circuit.

2.3.2.3.5 Use of design lines: In some cases where there are multiple areas of ablation and idiopathic scar, circuits can be complicated and placing a design line can be a useful visual aid.

2.3.2.3.5 Importing old studies: CARTO3 v4 allows maps from previous studies (Study > Load Maps from Previous Study) to be imported into the current study and viewed simultaneously, live, adjacent to the active map. This allows the operator to view the location of previous ablation lines. In more complex circuitry, this may prove helpful in trying to fathom some of the more complex wavefront patterns which might take some unexpected bend or stop abruptly around areas of iatrogenic conduction block.

2.3.2.4 Avoiding errors with a Ripple Map

A single entrainment after making a diagnosis with the Ripple Map can be reassuring in complex circuits. In complex cases, the potential for dual loop re-entry is relatively common. In these situations ablation of the clinical tachycardia may cause a small change in cycle length when transitioning to the bystander circuit. Unless a multi-electrode catheter, such as a coronary sinus decapole, shows a change in activation pattern, the transition may not be appreciated. Therefore, periodic checking of the cycle length is recommended and if the tachycardia has not terminated after an appropriate number of lesions delivered, a localised re-map with dense acquisition around the region of interest using RM can determine whether the tachycardia has changed.
Finally, if the. bars are moving out of sequence around the chamber randomly, check the cycle length and fiducial reference for changes as the map is unlikely to be interpretable.

2.3.4 GROUP 2 (CARTO ISOCHRONAL ACTIVATION MAP)

This will be according to standard practice of the operator. Entrainment can be used to guide the appropriate chamber to map. Points are collected using ConfiDENSE continuous mapping and auto-annotation unless the operator deems otherwise. Further manual annotation can be performed as appropriate. When the operator is satisfied adequate number of points have been collected, the time and number of point is noted and a diagnosis is made.

2.3.5 Categorisation of maps

Grade I map - High diagnostic confidence with clear patterns of activation evident; and operator selects optimal ablation site from the map.

Grade II map - Moderate diagnostic confidence with some regions where activation is not clearly seen; a single entrainment site requested before first ablation

Grade III map - Low diagnostic confidence and alternative arm (Ripple/Conventional activation) or multiple entrainment requested before first ablation

Grade IV map - Non-diagnostic despite all attempts.

Uncategorised - AT terminated or changed during point collection/pacing

3 STUDY OUTCOME MEASURES

PRIMARY ENDPOINT	1) Tachycardia change/termination with first ablation set after map categorisation .
SECONDARY ENDPOINT	1) Tachycardia change/termination during point collection
	2) Tachycardia change/termination during pacing manuoevre
	3) Failure to ablate/ change tachycardia with ablation.
	4) The need for entrainment mapping.

If tachycardia does not change with the proposed ablation lesion, or changes to another tachycardia, then operators can continue mapping and performing ablation in the patient's best interests.

If the tachycardia changes prior to the first ablation set, or in the event of a grade 3 diagnosis, operators can continue proceed as per individual preference.

3.1 Post ablation map in patients with any linear lesion sets:

The method for confirming block along a linear lesion line is according to operator preference

3.2 FOLLOW UP

As we are only studying the acute end point of tachycardia termination, no long term follow up data is required. Patients will be followed up as is routine in their Electrophysiology clinic outside of the research protocol. Any redo procedures over the subsequent year should be reported to the trial management team.

4. DATA ANALYSIS

The following data will be assessed:

Mapping:

1. Number of points

Tachycardia:

1.The diagnosis is recorded as either focal (localized reentry) or macro-reentry
2. The grade of diagnostic confidence is recorded
3. Validation of the diagnosis with change of activation/termination with ablation.
4. Number of times entrainment performed

Ablation:

1. Location of ablation delivery
2. The duration of RF before tachycardia change/termination

5. PARTICIPANT ENTRY

5.1 PRE-REGISTRATION EVALUATIONS

The direct care team will identify potential study patients against inclusion and exclusion criteria, before the Investigator determines their eligibility for participation. The Investigator will discuss the rationale for the study, study procedures, risks and benefits and all other issues mandated by the consent process. The potential participant will be offered an opportunity to participate in the study and written informed consent will be obtained if they agree. Study procedures and assessments will only be performed after written informed consent has been obtained. Patients recruited to this study will not need to undergo any additional investigations above what is required for a standard AT ablation procedure. The informed consent process and all study assessments will be documented in the patient's medical notes and study case report forms.

5.2 INCLUSION CRITERIA

To be eligible for the trial, subjects must meet all of the following criteria:

1) Patients undergoing ablation of sustained atrial tachycardia (post AF ablation) using 3D mapping.
2) Age range 18-85yrs.
3) Signed informed consent

5.3 EXCLUSION CRITERIA

Subjects with any of the following will be excluded from the study:

1. Patients with typical flutter.
2. Patient with non-sustained atrial tachycardia
3. Contraindication to catheter ablation
4. Unable to give informed consent

5.4 WITHDRAWAL CRITERIA

If patients lose the capacity to consent or wish to withdraw voluntarily, then they will be excluded from the study from this point. If the patient has agreed on the consent form, any data collected up to this point will be included in the data analysis.

6. ADVERSE EVENTS

6.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

Results in death

Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

Requires hospitalisation, or prolongation of existing inpatients' hospitalisation

Results in persistent or significant disability or incapacity

Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

6.2 REPORTING PROCEDURES

All adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed. As the patients are undergoing clinically indicated procedures any questions concerning adverse event reporting will be directed to the main clinical departmental lead and clinician supervising the case in the first instance.

6.2.1 Non serious AEs

All such events, whether expected or not, will be recorded.

6.2.2 Serious AEs

A SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to non-cardiac conditions, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

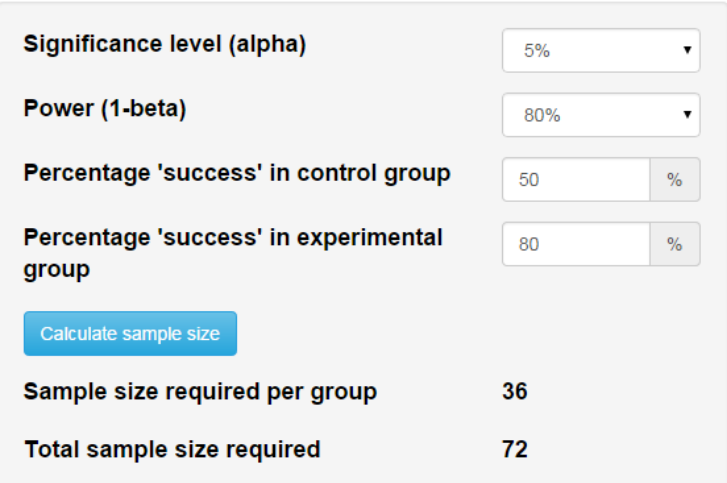
- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

7. STATISTICS

Sample Size:



Our retrospective study demonstrated a diagnostic yield using RM compared to standard CARTO activation maps of 80% vs 50% (Jamil-Copley et al. 2013). Assuming the same outcome measures, this study is designed to be sufficiently large to detect a difference between arms with 80% power, at the 5% two-tailed significance level. This requires a 36 patients in each group to give a minimum sample size of 72 patients. We have elected to recruit a total of 100 patients into the study.

Categorical variables will be expressed as percentages. Continuous variables will be expressed as mean ± 1 standard deviation for parametric data and/or median ± interquartile range for non-parametric data. The 2 groups will be compared using a student's t-test for parametric data and Mann-Whitney U-Test for non-parametric data. A value of $p<0.05$ will be considered significant.

8. DATA MANAGEMENT AND QUALITY CONTROL

The complete dataset will be collected for all patients who are randomised into the trial. The signed, original informed consent forms and the documentation of all study procedures and assessments will be kept in the patients' study notes. All data will be transferred to the study co-ordination centre with all appropriate supporting documentation as required such as hospital reports or imaging reports with all patient identifiers removed. Patients study documents will be identified by their study-specific patient number allocated at randomisation.

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

Ethical approval for this study was granted by the NRES Committee London – Fulham on the 3rd December 2014.

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. Ethics and R&D approval

letter will be required by the Study Co-ordination Centre before accepting participants into the study.

9.2 CONSENT

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so will be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.4 INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

9.5 SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.