How can NWSTC help MediTech SME provide evidence to develop devices for approval and comissioning

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NWSTC Director

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Liverpool Clinical Trials Unit

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WITH SUPPORT FROM THE ROSETREES TRUST

NHS National Institute for Health Research

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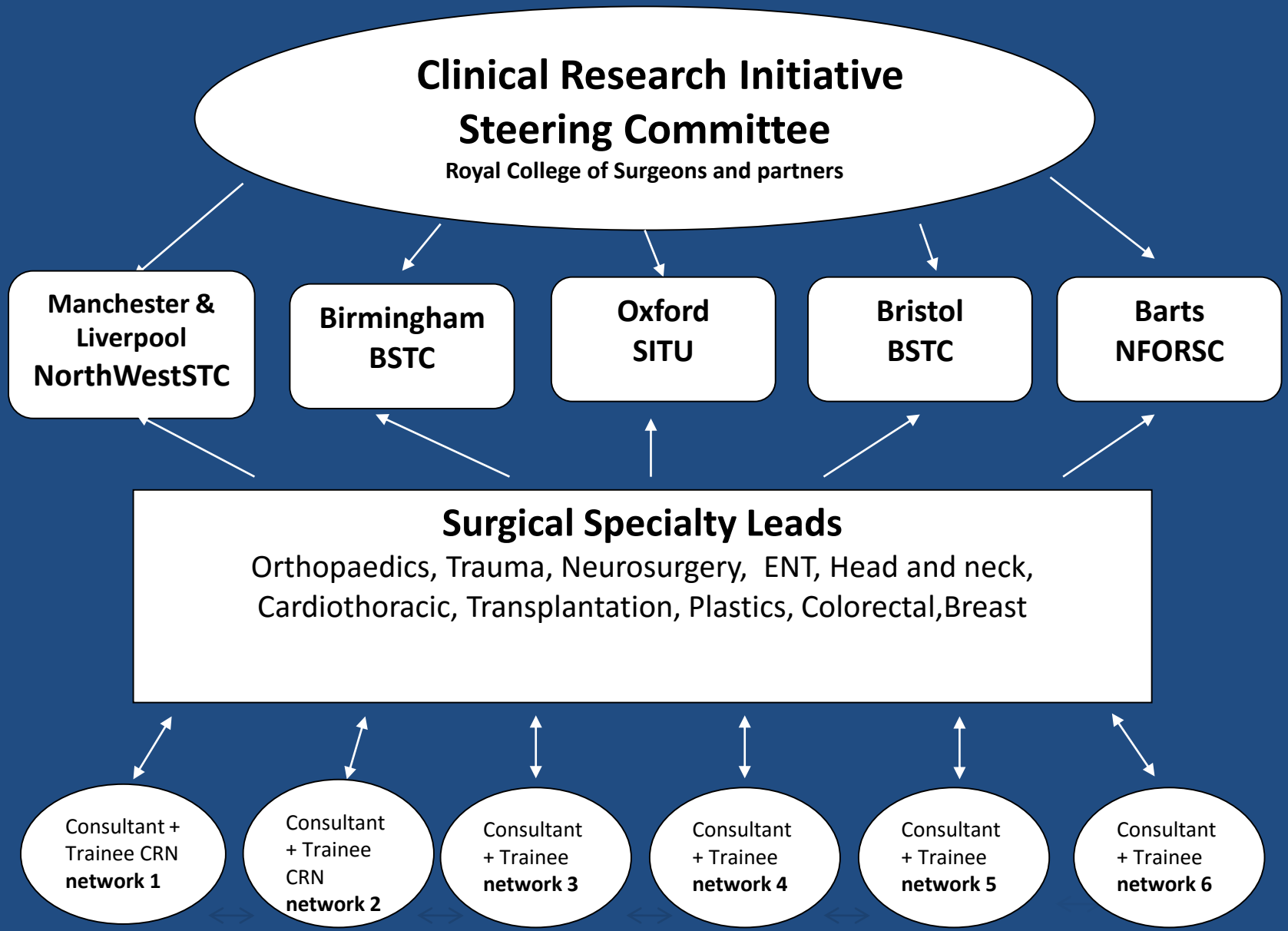

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North-West Surgical Trials Centre

- CLRN: North West Coast, Greater Manchester and (North)West Midlands
- 8 million population
- Expertise in: breast, vascular, colorectal, pancreas, head and neck, neurosurgery, orthopaedics, paediatric, plastic surgery
- 33 CIs, linked to over 90 national centres
- 3 NIHR Senior Investigators (1 Acad Med Sci)
  24 surgical ACF/ACL, 2 NIHR CS mentors

Liverpool Cancer Trials Unit

CTRC Clinical Trials Research Centre

Manchester Academic Health Science Centre (MAHSC) Trials Unit

MRC Hubs for Trials Methodology Research North West Hub

LCTU Liverpool Cancer Trials Unit

University of Liverpool

RCS North West Surgical Trial Unit with support from the Rosetrees Trust

Manchester 1824 The University of Manchester

Cancer Research UK

Medical Devices - CE marking

- A **medical device** is an instrument, apparatus, implant, in vitro reagent, or similar or related article that is used to **diagnose, prevent, or treat disease** or other conditions through a combination of mechanical, electronic and chemical biochemical action(s)
- Medical device can be assisted by pharmacological process i.e. drug-eluting stents
- Medical devices must have **a CE mark** for use within the EU, covered by the Directives:
  - Medical Devices Directive (93/42/EEC)
  - Active Implantable Medical Devices Directive (90/385/EEC)
  - IVDMDD – In Vitro Diagnostic Medical Devices Directive (98/79/EC)
- Manufacturer makes the initial assessment to determine the classification of their product and carry out the appropriate **conformity assessment** to obtain a CE mark.

MDB Class	Risk	Examples
Class I	Lowest risk	Surgical instruments, culture media
Class II	Low risk	Contact lenses, epidural catheters, pregnancy test kits, surgical gloves, ultrasound scanner
Class III	Moderate risk	Orthopaedic implants, glucose monitors, dental implants, haemodialysis systems
Class IV	High risk	HIV test kits, pacemakers, angiographic catheters

Clinical Investigations with Medical Devices

- Within EU, high-risk devices had to **establish safety and performance** with no need to prove they made a difference to patients.
- With the number of devices being recalled, the current Medical Device Directive (MDD) was reviewed.
- The new MDD requires clinical data on efficacy preferably obtained through randomised controlled trials (RCT) before marketing approval.
- Already standard for new medicines but new for medical devices

EU Texts enter into force 20 days after publication in EUOJ: **25 May 2017**
Full application for Medical Devices Regulation: **26 May 2020**
Full application for the IVD Regulation: **26 May 2022**

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Device Trials Are Unique

- Usually smaller than drug trials
- Some novel, many “me too”
- Challenges with blinding, randomisation and control
- Influence of physician control
- Device modifications during the feasibility phase trial
- Endpoints = highly diverse
- Typically, feasibility stage(s) lead to single pivotal trial.
- Designed to support a “reasonable assurance of safety and effectiveness” for the marketing application

Device Feasibility Studies

- Support for a future pivotal study or answer basic research questions
- Not intended as primary support for a marketing application
- Endpoints and sample size generally not statistically driven
- Often required by the MHRA prior to pivotal study to assess **basic safety and potential for effectiveness**
- Generally approx. 10-40 patients (but may be larger)
- MHRA review is primarily focused on safety and whether the potential benefit or value of the data justifies risk

MHRA Feasibility IDE Review

- Focus on safety
- Critical issues
  - Reasonable study conceptuality?
  - Adequate pre-clinical validation of device?
    - Why is clinical study really the next necessary step?
  - Appropriate mitigation of potential risks?
  - Appropriate enrolment criteria?
  - Patients adequately informed?
  - Sample size appropriate?

Device Pivotal Study

- Generally intended as the primary clinical support for a marketing application
- Designed to demonstrate a “reasonable assurance of safety and performance(effectiveness)”
- Endpoints and sample size are statistically driven
- Designed to assess both safety and performance
- MHRA review is much more complex

Pivotal Study Endpoint Design

- Should evaluate the safety and effectiveness of the device in the population expected to be indicated

- Generally divided into:
  - 1 or more “safety” endpoints
  - 1 or more “effectiveness” endpoints

- A study would be considered successful if both the safety and effectiveness endpoints are met

Does Study Success Imply Device Approval

- Often but not always

The primary endpoints may not capture a serious unexpected safety concern observed in the trial

- Other clinical or non-clinical data may conflict with the study result
- Can result in:
  - Device disapproval
  - Requirement for more data
  - Limited indication

NWSTC :-Evaluating Surgical Devices

Dedicated trials units expertise

to develop or evaluate new Devices and provide evidence for NHS/NICE

- Provide Scientific expertise, Statisticians, trial methodologists, Health Economists and QoL experts (to develop grant applications to obtain funding).

– Surgical Specialty Leads

- Engaged Clinical Leadership in each discipline and proctoring.

– Clinical Research Networks(funding/support)

- Delivering multicentre trials via NIHR Portfolio

Surgical Technology Evaluation Portal (RCS/NOCRI)

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Conclusions - One size does not fit all for device trials

- **Pivotal studies**: design to evaluate whether is a "reasonable assurance of safety and effectiveness"
- Approvability: based upon a benefit-risk assessment which considers outcome of primary safety and effectiveness endpoints
- Secondary endpoints are used to support claims if the primary endpoints are successful
- All endpoint analyses and definitions should be clearly pre-specified in the approved clinical protocol
- NWSTC can help with Trial design and funding applications . Recommend talking to the MHRA early in the pre-submission process.

Surgical Device Trials

- Joint Replacement
- Open Heart surgery
- Microsurgery – Plastic surgery
- Cochlear implants
- Endoscopic Surgery
- Laparoscopic/minimally invasive surgery
- Sentinel Node Biopsy in Breast Cancer

NIHR-STC

- **BEA – bioimpedance**
- **SentiMag**
- **ESSBR – Strattice**
- WOLLF
- TISU
- PACE
- HubBLe
- Amaze
- TERSC
- ROCSS
- ReDUCe
- **PICO NWPT**
- **PPAC**
- Fracture Fixation Ankle Surgery
- eThoS
- **CReST**
- CCRN 2404
- CCRN 2109
- BY-BAND

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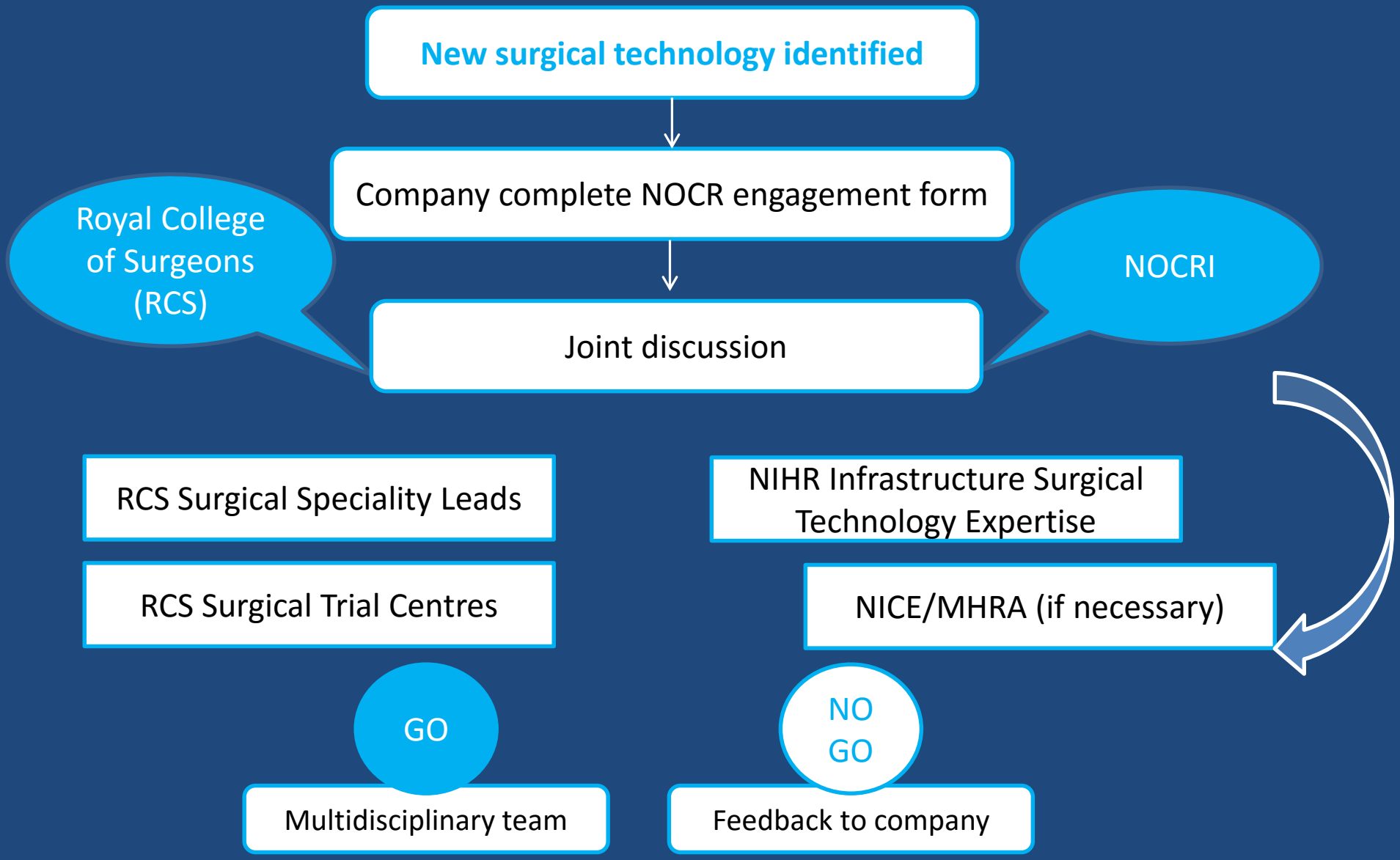
Surgical Technology Evaluation Portal



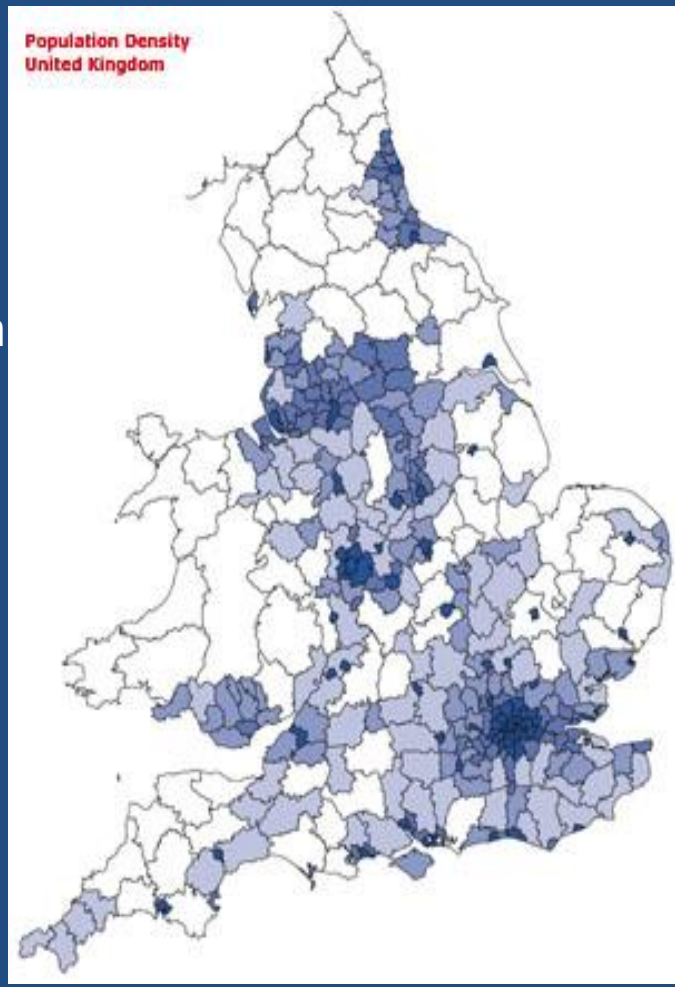
North-West Surgical Trials Centre

- Collaboration of 3 NW Trials Units and Surgical CI including:
  - LCRN and Clinical Trials Leadership
  - MRC NW Hub for Trials Methodology Research

- Spans 5 counties (inc N. Staffs): approx 8m population

- 25 NW Surgical C.I.(36 Trials) linked to 90+ centres:

- Broad General Surgery/Surgical Oncology trials
  - International Leadership in H and N Surgery (OFMS,ENT, Craniofacial, Neurosurgery), Pancreatic and Breast Ca.



- 3 NIHR Senior Investigators (1 Acad Med Sci)
  17 surgical ACF/ACL, 2 NIHR CS mentors
  ACF/ ACL = 17, Surgical Trainees Collaborative =2

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MedTech Funding-Why apply to i4i?

NHS National Institute for Health Research

- Dedicated Medtech funding programme
- Uncapped awards
- Source of early funding for SMEs
- Risk oriented programme
- Commercially oriented panel supported by peer review
- Milestone-based awards to de-risk
- Guidance and advice
- Favourable independent review by RAND[1]

1 'The NIHR Invention for Innovation (i4i) programme. A review of progress and contributions to innovation in healthcare technologies'

Challenges in Designing Clinical Investigations of Medical Devices

- **Limitation in comparative trial design (e.g., an implanted device):**
- Comparative clinical trials precluded due to ethical considerations. Often historical controls in the study or patients as their own controls (pre- and post-surgery) required to evaluate outcome

- **Limitation with Device:**
  - Some endpoint definitions in device trials may vary from device to device (e.g., AF burden calculation)
  - Memory capacity leads to missing episodes and to inaccurate information
  - Device date stamp resets may lead to inaccurate information re: endpoints

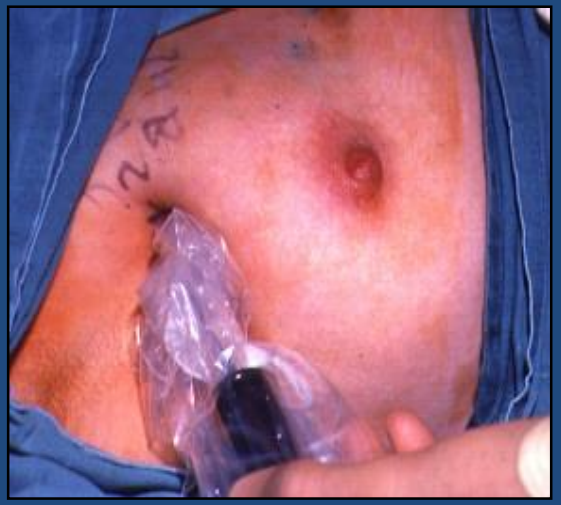
Submission Elements, Pivotal IDEs

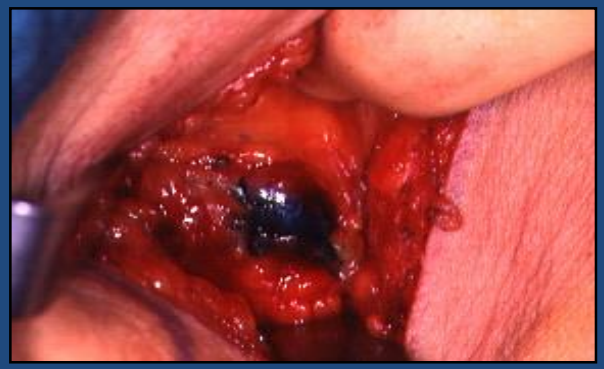
- Primary and secondary endpoints
  - Discussion of appropriateness of endpoint parameters, hypotheses and success criteria

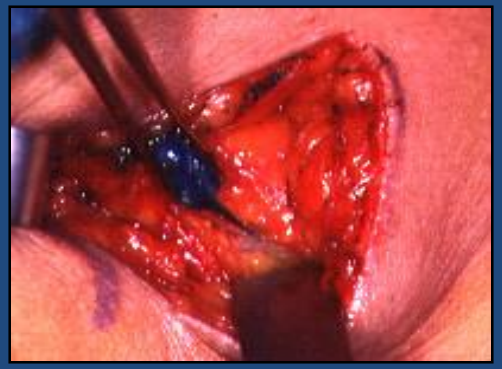
- Basic trial design
  - Controlled? (If not, why not?)
  - Randomised? (If not, why not?)
  - Blinded? (If not, why not?)

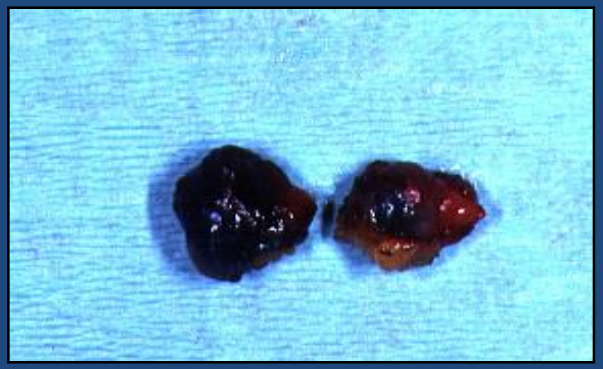
Sentinel Node Biopsy

Introduction needed Proctorship phase to teach new technique

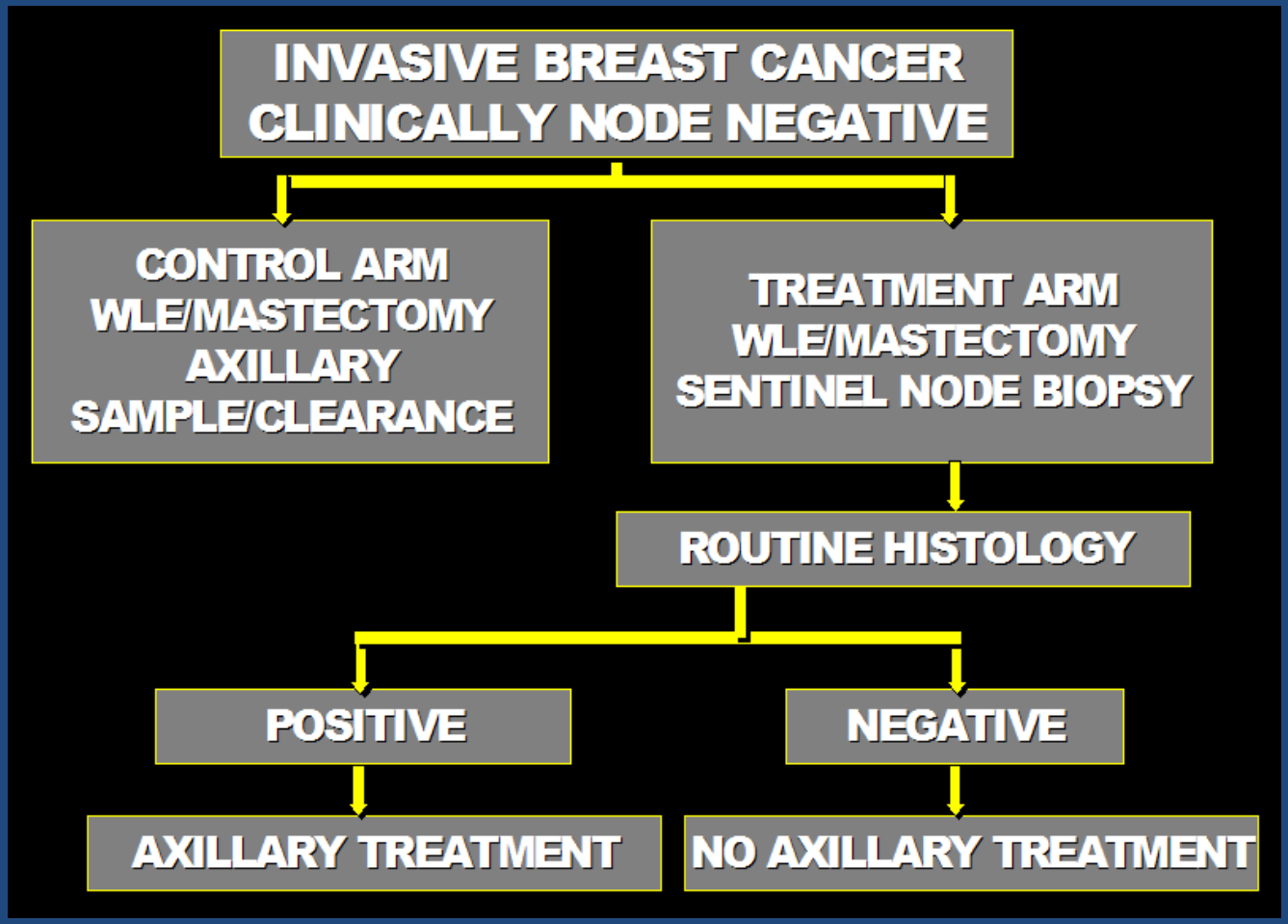








ALMANAC Randomised Phase



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Sentinel Node Biopsy in Breast Cancer

516 evaluable pts – all isotope alone (5-10 Mbq of technetium/albumin)

96% detection rate

- Axillary pain: SNB 8% v 39% Clearance
- Numbness: 2% v 85%
- Arm swelling >1 cms: 0% v 37%

No difference in axillary recurrence at 5 years

Phases of Development for Study of Surgical Techniques

- **Phase 0 Proof of principle**
- **Phase 1 Refinement and definition**
- **Phase 2 Dissemination**
- **Phase 3 Comparison with current standard treatment**
- **Phase 4 Surveillance and quality control**

McCulloch, JRSM 2008

Basic Submission Elements

- Risk analysis
  - What are the potential risks to the patient?
  - Does the study mitigate the risks where possible
  - Are the risks out-weighed by the potential for benefit and/or value of the study?
- Patient monitoring and follow-up plan
- Inclusion and exclusion criteria
- Informed consent document
- Sample size and number of investigational centres, with justification

Achievements of Surgical Research

- Joint Replacement
- Open Heart surgery
- Microsurgery – Plastic surgery
- Electrostimulation - cochlear implants
- Endoscopic Surgery
- Laparoscopic/minimally invasive surgery
- Sentinel Node Biopsy in Breast Cancer

All “Device Trials”

Key changes to EU Medical Device Legislation

Notified Bodies

- Strengthened designation criteria
- Joint audits: 3 Member States and Commission (FHAA)
- Unannounced audits

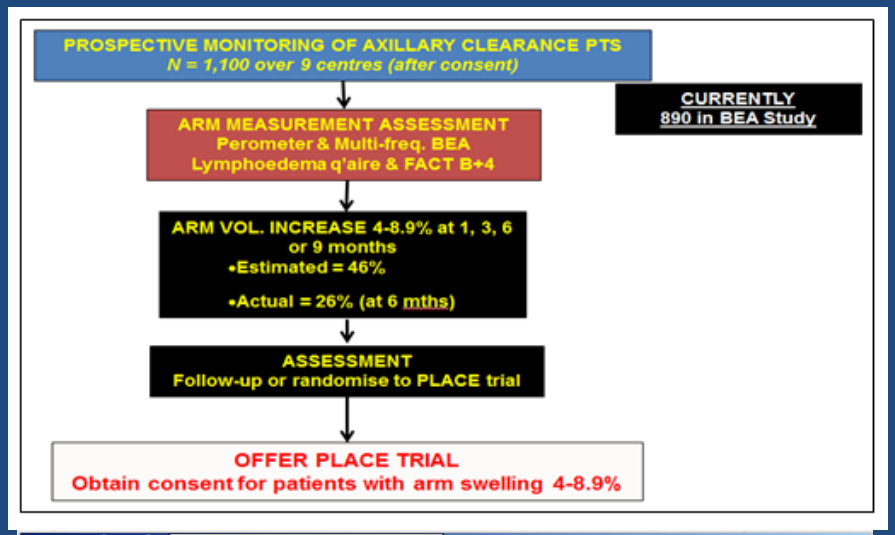
Clinical evidence

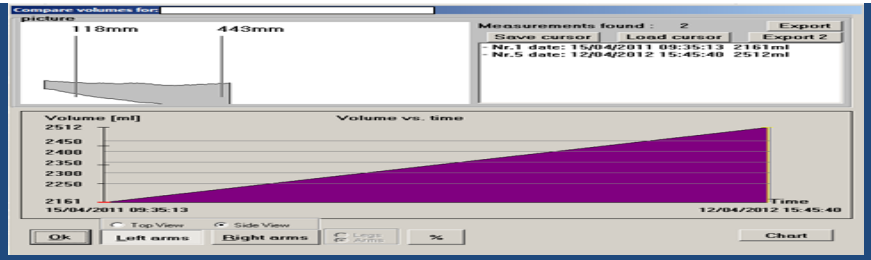
- Less equivalence, more data for high risk devices
- Publish Safety and Performance data
- Post-market clinical follow-up

Pre-market

- Scrutiny for high risk devices
- Common Specifications
- Responsible person for manufacturers and Authorised Representatives

BEA Study:Prospective Comparison of Multi-Frequency Bioimpedance with Perometer Measurements in the Detection of Lymphoedema after ANC





Bioimpedance

Perometer

Study of diagnostic Sensitivity/Specificity vs Lymphoedema Endpoints at 2 and 5 years

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ROSSINI

Reduction Of Surgical Site Infection using a Novel Intervention

A randomised controlled trial of a wound-edge protection device to reduce surgical site infection

Inclusion: All patients undergoing laparotomy

Exclusion: Laparoscopic-assisted surgery

Online randomisation 1:1 intervention v control

Blinded wound reviews pre-discharge (5-7 days) and at 30-33 days post-op

Quality of life and **resource usage data** also collected

Funded by NIHR Research for Patient Benefit programme

UNIVERSITY OF BIRMINGHAM

WM RESEARCH COLLABORATIVE

PC-CRTU