The IDEAL template and specific opportunities

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WHAT IS IDEAL?

An integrated evaluation pathway

REGISTRATION OF 1st in MAN (Stage 1)

PROSPECTIVE DEVELOPMENT STUDY (Stage 2a)

PROSPECTIVE EXPLORATION STUDY (Stage 2b)

RCT (Stage 3)

REGISTRY (Stage 4)

Why was IDEAL needed?

- 1990s: Evidence Based Medicine movement began to demand rigorous evaluation of therapies
- EBM doctrine: strongly focussed on the Randomised Controlled Trial (RCT)
- Surgeons criticised for their inability to comply
- This helped to expose the real difficulties of RCTs of complex interventions

EBM and the Pharma Paradigm

PHARMA PARADIGM

- Theory
- Lab demonstration
- (animal studies)
- First-in-man study
- Toxicity study (Phase I)
- Efficacy Study (Phase II)
- RCT (Phase III)
- Post-Marketing Surveillance (Phase IV)

- Clinical Drug development follows a relatively simple pathway because:
  - Modifications of the treatment other than dose adjustment are rare
  - Most modification is done in laboratory studies before patients become involved

ANALYSIS: 5 REAL BARRIERS TO SURGICAL RCTs

1. Need for iterative adjustment and refinement of technique in clinical practice
2. Need for definition of technique which encompasses reasonable variation
3. Variation in delivery (need to evaluate learning curves, specify quality control)
4. "equipoise" difficulties for the Clinician

   a. Intimately involved with the technique – unable to be objective

   b. (?surgical personality – naturally decisive people find equipoise uncomfortable)
5. "equipoise" difficulties for the Patient
   - Decision to undergo surgery usually irreversible and risks may be grave
   - Relationship of trust with surgeon – tendency to accept expert view (even if not explicit)

IDEAL Framework

A 5 stage description of the journey of surgical innovation

- Stage 1 - **I**DEA
- Stage 2a - **D**EVELOPMENT
- Stage 2b - **E**XPLORATION
- Stage 3 - **A**SSESSMENT
- Stage 4 – **L**ONG TERM MONITORING

IDEA (Stage 1)	DEVELOPMENT (2A)	EXPLORATION (2B)	ASSESSMENT (3)	LONG TERM STUDY (4)
Initial report	"Tinkering" (rapid iterative modification)	Technique now more stable	Gaining wide acceptance	Monitoring late and rare problems, changes in use & quality of surgical performance
Innovation may be planned, accidental or forced	Small experience from one centre	Replication by others	Considered as possible replacement for current treatment	
Focus on explanation and description	Focus on technical details and feasibility	Focus on adverse effects and potential benefits	Comparison against current best practice (RCT if possible)	
		Learning curves important		
		Definition and quality parameters developed		

Key Questions at each IDEAL Stage

Each stage is defined by one key issue:

STAGE 1: What is the new treatment concept?

STAGE 2a: Have we perfected it?

STAGE 2b: Can we agree on what it is and who should get it for the purposes of an RCT?

STAGE 3: Is it better than current practice? (RCT if possible)

STAGE 4: Are there any surprises?

Implications of the Key Questions

- Studies at each stage should be designed to answer the key question
- IDEAL Recommendations describe study formats designed to do this

The IDEAL Recommendations

- Idea (First in Man) 1.
  - Complete technical description
  - Explanation of patient selection
  - Registration of report
- Development 2a.
  - Prospective Cohort Study (PDS)
  - Transparent Consecutive Reporting of Cases
  - Explanation of Changes in Technique, Indication
- Exploration 2b.
  - Prospective collaborative cohort study (PES)
  - Evaluation of learning curves
  - Definition of QC parameters
  - Estimation of power calculations
  - Early joint analysis leading to RCT
  - Feasibility/Pilot RCT
- Assessment 3
  - Definitive RCT
  - Removal of investigator bias from recruitment
- Long Term Study 4
  - Registry to detect late/rare events
  - Monitoring of indication and performance creep

Stage 2a: Prospective Development Studies

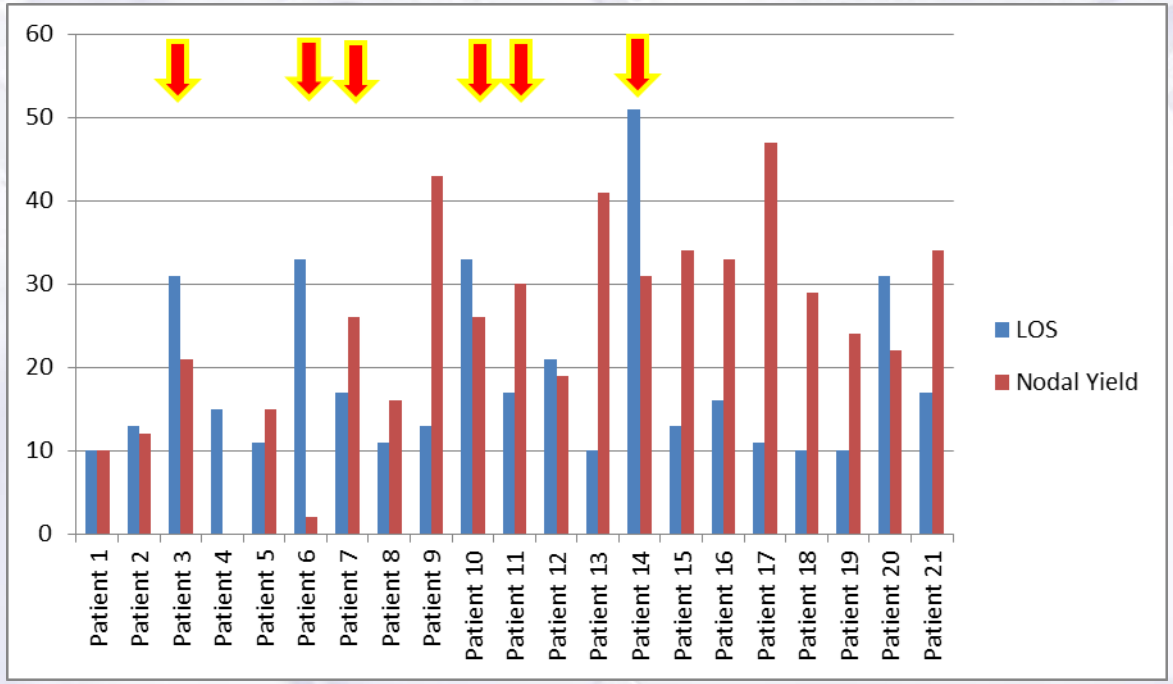
- ***Key Specific Recommendations***:

  - Detailed technical description of procedure
  - Detailed description of patient selection criteria
  - Description of ALL modifications, when made in the series, and why
  - Prospective account of ALL cases consecutively, showing results

PDS Example:
Development of Robotic Oesophagectomy

Arrows show 6 specific modifications to technique, described in the paper:

Modification 3 seems to improve nodal yield.



Diez del Val I, Loureiro C, McCulloch P. Int J Surg. 2015 Jul;19:104-11. doi: 10.1016/j.ijsu.2015.04.035.

Why do Development studies?

- Techniques in DEVELOPMENT stage are not yet stable
- Reporting changes and their reasons allows others to learn faster and not repeat mistakes
- Therefore this approach is ethically superior to current practice
- Usually small numbers of cases, so will not slow development process or increase costs.

Stage 2b: Prospective Exploration Study

Key Recommendations

(collaborative prospective cohort study)

- **To evaluate technique prospectively and co-operatively**
- **To agree procedure *definition*, *quality* standards & *patient selection criteria***
- **To accumulate *data* for *power calculations***
- **To evaluate *learning curves***
- **To evaluate *preferences* and *values* amongst patients and clinicians**
- **To achieve consensus on future *trial question and comparator***
- **To develop a multi-centre randomised trial**

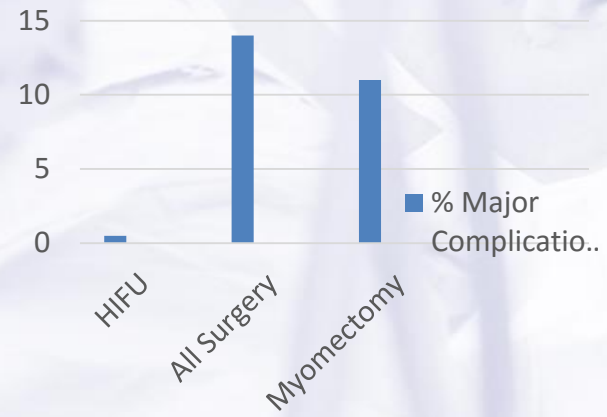
PES example: HIFU for fibroids

Chen J, Li Y, Wang Z, McCulloch P, Hu L, Chen W, Liu G et al. Evaluation of HIFU Ablation for UterineFibroids: an IDEAL Prospective Exploration Study. BJOG. 2017 Apr 19. doi: 10.1111/1471-0528.14689.

- Previous papers show progress of technology through stages 1 and 2a
- 20-centre prospective cohort offering surgery OR HIFU (patient choice)
- Tight definition of HIFU treatment
- learning curves measured
- Quality control assured
- Used results to plan RCT protocol

HIFU Exploration study results

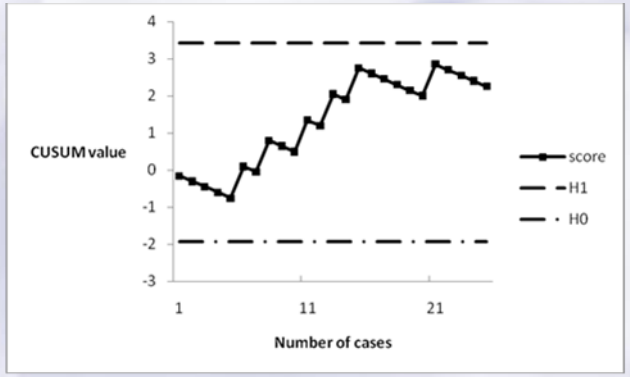
Significant Complications



Patients treated

- Hysterectomy 472
- Myomectomy 586
- HIFU 1353

	Hospital Stay (days)	Return to Work (days)
HIFU	3.63	4.07
Myomectomy	8.96	24.01
Hysterectomy	10.53	29.49



Learning Curves analysed

These results don't scientifically prove the superiority of HIFU, but make it clear that an RCT using these outcomes could not be done, for lack of equipoise.

Why do Exploration (2b) studies?

- Organising surgical RCTs is difficult: it requires TRUST and UNDERSTANDING between surgeons
- 2b studies improve trust and understanding by improving joint ownership and belief in data
- 2b studies allow questions which hold up agreement on RCTs to be answered, e.g.
  - Which variations of the procedure are acceptable?
  - Are some colleagues still learning?
  - Which patients are suitable?
  - How many patients will we need?
  - What questions are important to patients – and surgeons?
- In this way 2b studies should improve the FEASIBILITY of RCTs
- Sometimes 2b studies may alternatively show that an RCT is not feasible

What about RCTs: What 2b will have done for you!

- Agree clear definition of the procedure and permissible variation ✅
- Agree clear QC measure for delivery of the procedure ✅
- Agree on inclusion and specific analysis of patient subgroups of special interest or concern. ✅
- Identify whether operating team learning curves need to be considered +/- eliminated ✅
- Develop evidence-based effect estimate with narrow CI for power calculations ✅

IDEAL RCTs

- Use standard well-validated and widely recognised definitions for measures of outcome, patient characteristics and other confounders
- Use qualitative approaches such as QUINTET to align outcomes with values of patients and investigators
- Remove investigator bias from the consent process using trained nurses or decision aids
- Adjust level of pragmatism in design using PRECIS-2
- Report using CONSORT extension for complex interventions and TIDIER checklist for reporting outcomes

Other sources of Level 1 Evidence

- Expertise-based RCTs
- Cluster-randomised trials
- Stepped Wedge designs
- N of 1 studies
- Controlled Interrupted Time Series

Beyond RCTs: IDEAL Stage 4 & Registries

- Registries can be a resource for developing trials (TWICS)
- Registries are only useful if they are comprehensive. Therefore:
  - They should be kept as simple as possible
  - Sampling verification of data is essential
  - Feedback & other incentives to take part need careful design
- Registries are the best study design for evaluating:
  - late or rare treatment effects
  - Indication creep
  - Changes in performance over time

Using IDEAL in surgical research

- Easy to identify IDEAL Stage by PubMed review (Pennell et al)
- IDEAL 2a studies usually quick and simple (and cheap)
- IDEAL 2b studies can be front-loaded onto grant proposals for an RCT – enhance the feasibility of the trial
- Journal editors considering guidelines
- Revised and extended Recommendations out this year
- Join the Collaboration!