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Looking ahead:
From N of 1 To N of Many

Tim Yu, MD, PhD
Co-Founder, N1C
Division of Genetics & Genomics
Boston Children's Hospital / Harvard Medical School

The problem

- *Individualized medicines: from N of 1 to N of many*

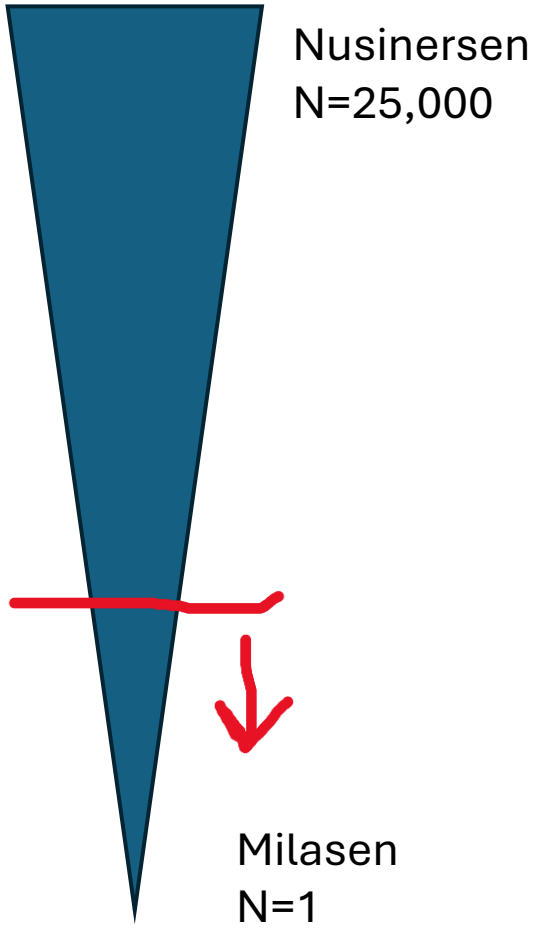
- *We've demonstrated that this is* ***possible***
- *We're beginning to explore whether this is* ***repeatable***
- *We need to plan ahead to make this* ***rigorous & scalable***

N=1 COLLABORATIVE

One, many, and in between

- *The extremes*
  - *N=1: traditional "trial" is* ***impossible***
  - *N=many: traditional "trial" is* ***imperative***

- *Anchor points in between?*
  - *N=5, N=50, N=500?*
  - *N=identifiable today? in the future?*
  - ***N="not currently commercializable"***



Platform trials?

- ***Basket & umbrella trial designs***
  - *One drug, several diseases (with common molecular etiologies)*
  - *Several drugs, one disease (stratified by molecular etiology)*
  - *E.g., Steric-blocking ASOs for A-T, allele-selective ASOs for KIF1A…*

- ***Easy to say, not easy to get there***
  - *Scientific factors: costs of designing, screening, safety testing*
  - *Regulatory requirements: 1 IND per molecular entity and/or patient ("N<=2")*

- ***A daunting task?***
  - *Even if we do get there, numbers may still be too small, outcomes too imprecise, heterogeneity too high*

N=1 COLLABORATIVE

Revisiting what this work is about

- *Orphan diseases*
- *Seriously debilitating / life-threatening conditions*
- *Patient-customized approaches → precisely targeted drugs*
- *Complex risk-benefit considerations → individually consentable*
- *Treatment, research, a hybrid of both*

Revisiting what this work is about

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Innovative medical care with iterative learning

A procedural / interventional / surgical model

"Interventional genetics"

N=1 COLLABORATIVE

Evidence-based surgery & the IDEAL framework

- IDEAL: a new paradigm for the evaluation of surgical operations, invasive medical devices and other complex therapeutic interventions.
- IDEAL began with a series of meetings at Balliol College, Oxford during 2007 to 2009 to discuss the specific challenges of evaluating surgical innovation, recognizing, analyzing, and proposing solutions for the challenges which arise as new procedures move from proof of concept towards a randomized controlled trial (RCT). These discussions resulted in the publication of a five-stage Framework describing the natural stages of surgical innovation (Idea, Development, Exploration, Assessment, and Longterm Study), together with recommendations for a rigorous stepwise surgical research pathway, and suggestions for appropriate study methodology for the questions which characterise each stage. This was subsequently followed up by publications offering methodological guidance.

McCulloch et al, 2009; Hirst et al, 2019

Motivation

- "Surgery is a complex intervention with properties which make it more difficult to evaluate rigorously than drug treatments. Evaluation methods that fail to address this complexity have led to much controversy and wasted effort through poor study design, inadequate reporting and failure to reach agreement on standards for high quality trials. The resulting adverse consequences have included widespread adoption of new techniques or devices which later proved to be harmful and of refusal by healthcare funders to reimburse for innovations with an inadequate evidence base, as well as large scale failures of surgical research to compete successfully for public funding.

McCulloch et al, 2009; Hirst et al, 2019

IDEAL: Why is it necessary?
Pharma paradigm doesn't fit surgery

- **Definition of the intervention**
  - Iterative changes
  - Acceptable variation
- **Delivery**
  - Learning curves
  - Quality control
- **Strong treatment preferences**
  - Loss of equipoise
  - Invasiveness, risk, permanence
- **Availability of treatments outside clinical trials**

Slides from Allison Hirst
IDEAL Collaboration, 2017

The IDEAL Collaboration

Idea, Development, Exploration, Assessment, Long-term follow-up

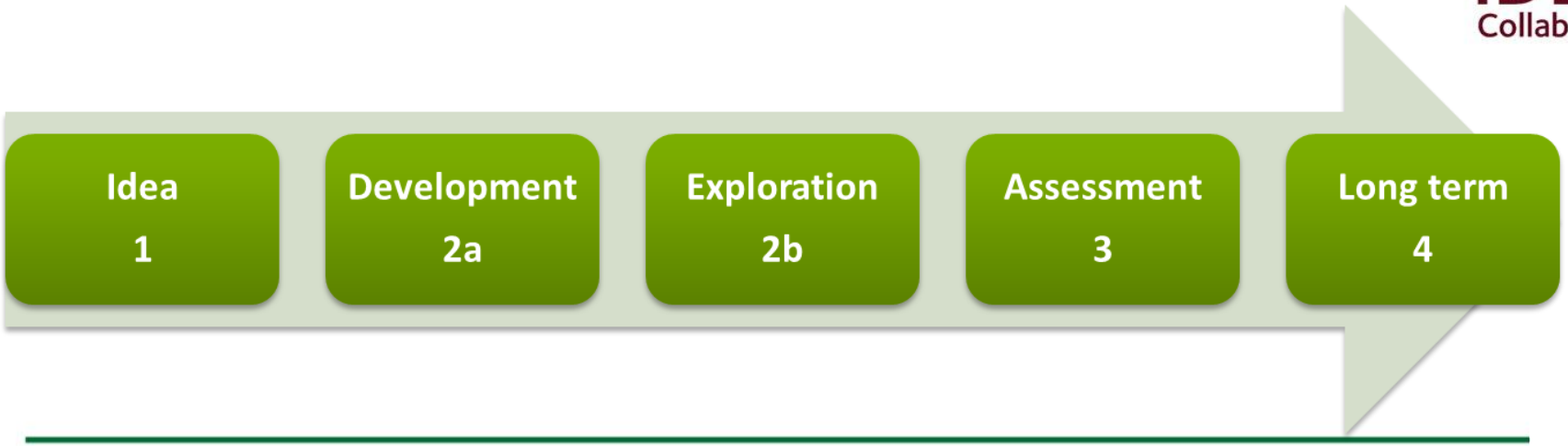
IDEAL Framework and Recommendations

Describes natural stages of development in surgery

Optimal study designs and research practices

Idea, **D**evelopment, **E**xploration,
Assessment, **L**ong-term follow up

IDEAL: An integrated evaluation pathway for surgical innovation



Surgical Innovation and Evaluation 3

No surgical innovation without evaluation: the IDEAL recommendations

*Peter McCulloch, Douglas G Altman, W Bruce Campbell, David R Flum, Paul Glasziou, John C Marshall, Jon Nicholl, for the Balliol Collaboration**

McCulloch P et al Lancet. 2009 Sep 26;374(9695):1105-12.

Slides from Allison Hirst
IDEAL Collaboration, 2017

IDEAL Framework – (I)dea

- **Idea**
  - Initial report
  - **"What is the new treatment concept? Is it possible?"**
  - Innovation may be planned, accidental or forced
  - Focus on explanation and description

McCulloch et al, 2009; Hirst et al, 2019

IDEAL Framework – (D)evelopment

- **Development**
  - Gaining experience in one or few centers
  - Focus on technical details, feasibility, rapid iterative modification of technique/indications ("tinkering")
  - **"Is it safe to pursue further? Is it worth pursuing further? Is the technique sufficiently stable to allow replication in more centers?"**

McCulloch et al, 2009; Hirst et al, 2019

IDEAL Framework – (E)xploration

- **Exploration**
  - Technique now more stable, with acceptable variation
  - Use expands to more centers
  - Prospective registry/cohort study with collaborative collection of a common dataset
  - **"Do we agree on the right technique, quality parameters, outcome measures, target population(s)? Are we prepared / can we prepare for a larger scale trial?"**

McCulloch et al, 2009; Hirst et al, 2019

IDEAL Framework – (A)ssessment and (L)ongterm monitoring

- **A**ssessment
  - Comparisons vs. current best practices in trials to consider establishing as new standard of care
  - **"Is new technique better or worse that what we do now?"**

- **L**ongterm monitoring
  - Monitoring late and rare problems, changes in use over time
  - **"How does it perform in the real world? What are the rare complications? Are indications changing?"**

McCulloch et al, 2009; Hirst et al, 2019

Stage 1: Idea

Key Question: "What is the new treatment concept /is it possible?"

- First-in-Human use of new surgical technique
- Planned or unplanned in an emergency - justify

Stage 1: Idea

Recommendations

- Report/publish
  - Patient characteristics – how selected
  - Detailed technical description (reproducible) – consider video
  - Pre and postoperative care
- Universal reporting (regardless of success)
- Liability and confidentiality? Intellectual property?

Slides from Allison Hirst
IDEAL Collaboration, 2017

Stage 2a: Development

- Single surgeon/centre gains experience (usually 10-20 pts)
- Focus on technique and changes made in response to outcomes

Key Questions:

- "Is it safe to pursue further?" - "Is it worth pursuing further?" - "Is technique sufficiently stable to allow replication in other centres?

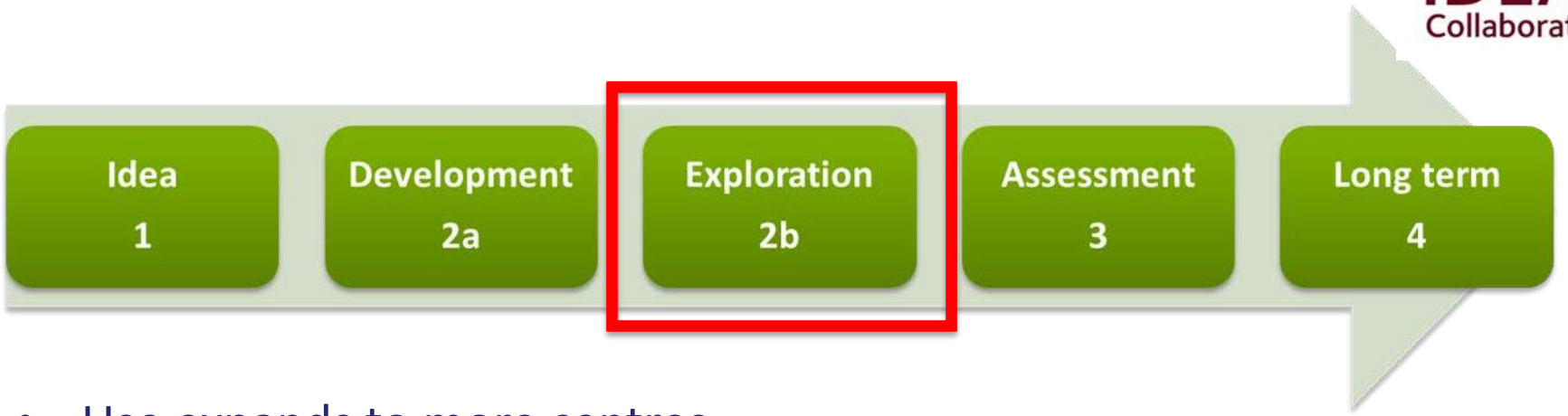
Stage 2a: Development

- Prospective Development Study - NOT a retrospective case series
- Prior protocol

Should report/publish:

- All patients considered for inclusion
- Detailed inclusion and exclusion criteria
- All consecutive patients short-term outcomes
- Evolution of technique is focus of report

Stage 2b: Exploration – bridge to a pivotal trial



- Use expands to more centres
- Technique stabilized with acceptable variation
- Larger dataset is accumulated

Key Questions:

- "Are we ready for a definitive RCT?"
- "Do we agree on the right technique and outcome measures?"
- "Can we do this well-enough?"
- "Can we explore and overcome barriers to feasibility?"

Slides from Allison Hirst
IDEAL Collaboration, 2017

Stage 2b: Exploration - bridge to a pivotal trial

Prospective Exploration Study

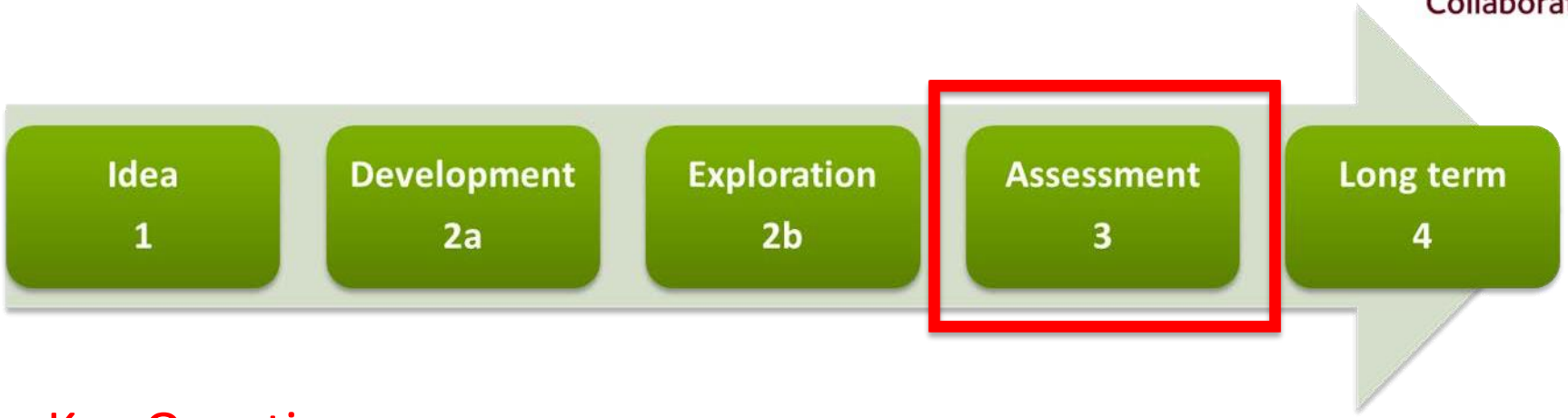
- Multi-centre prospective cohort study

Should report:

- Collaborative collection of a common dataset
- Evaluation of operator learning curves
- Attitudes towards the interventions—equipoise
- Confirm target population and primary endpoint for RCT

Slides from Allison Hirst
IDEAL Collaboration, 2017

Stage 3: Assessment



Key Question:

"Is new technique better or worse that what we do now?"

Formal evaluation against best current therapy

- RCT preferred

Slides from Allison Hirst
IDEAL Collaboration, 2017

Stage 4: Long-Term Study

Key Questions:

- "How does it perform in the real world?"
- "What are the rare complications?"
- "Are indications changing?"

Registries

80% of UK Bariatric surgeons participate

50,000 procedures included from 2009-2016

Slides from Allison Hirst
IDEAL Collaboration, 2017

Is IDEAL just for surgeons?

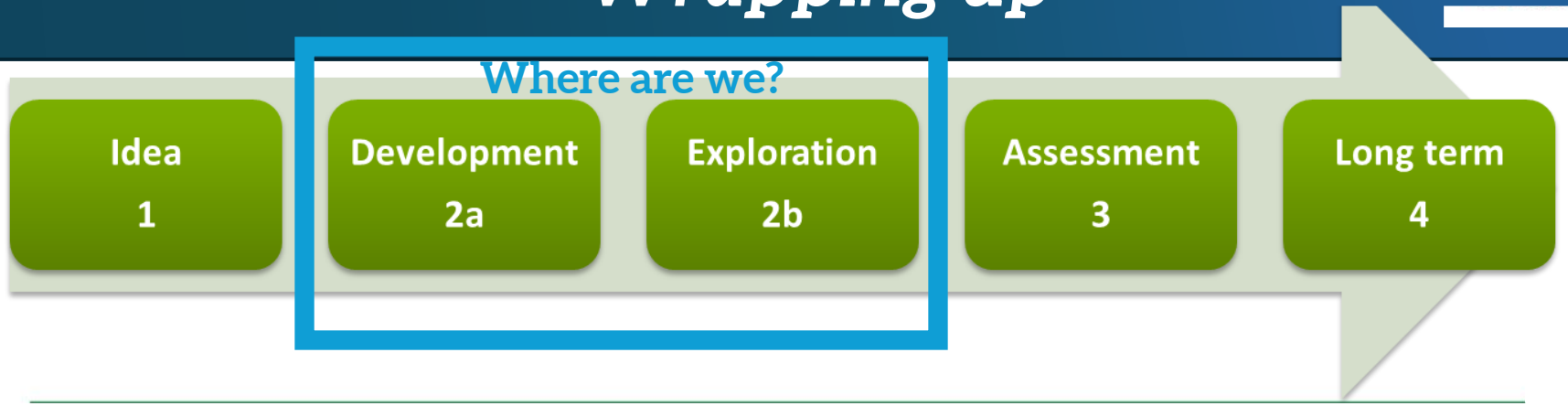
- 2a Development studies are appropriate wherever complex interventions require refinement in live settings

- 2b Exploration studies are appropriate wherever both the intervention and the threshold for acceptable quality of delivery require definition to allow meaningful comparisons

- COMPLEX THERAPIES
  - Endoscopic manoeuvres
  - Radiologically guided manoeuvres
  - Invasive therapeutic devices (**IDEAL-D**)
  - Physiotherapy (IDEAL-Physio)
  - Psychotherapy
  - Radiotherapy (IDEAL-R)
  - Quality Improvement projects
  - Complex public health interventions

Slides from Allison Hirst
IDEAL Collaboration, 2017

Wrapping up



Recommendations:

- Registration of protocols before study starts, with selection criteria & technical methods
- Prospective accounts of ALL cases
- Clear STANDARDIZED definitions of outcomes reported
- Collaborative collection of a COMMON dataset

McCulloch et al, 2009; Hirst et al, 2019

Wrapping up

- *Individualized medicines: from N of 1 to N of many*

- *We've demonstrated that this is **possible***
- *We're beginning to explore whether this is **repeatable***
- *We need to plan ahead to make this **rigorous & scalable***

- *While existing pharma models are not fit-for-purpose,* ***we need not start from scratch***