How to design clinical studies for small populations

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Introduction

- What information FDA needs to approve a new treatment
- How to select study endpoints
- A few important features of clinical studies

Everything you wanted to know …
… in 10 minutes or less!

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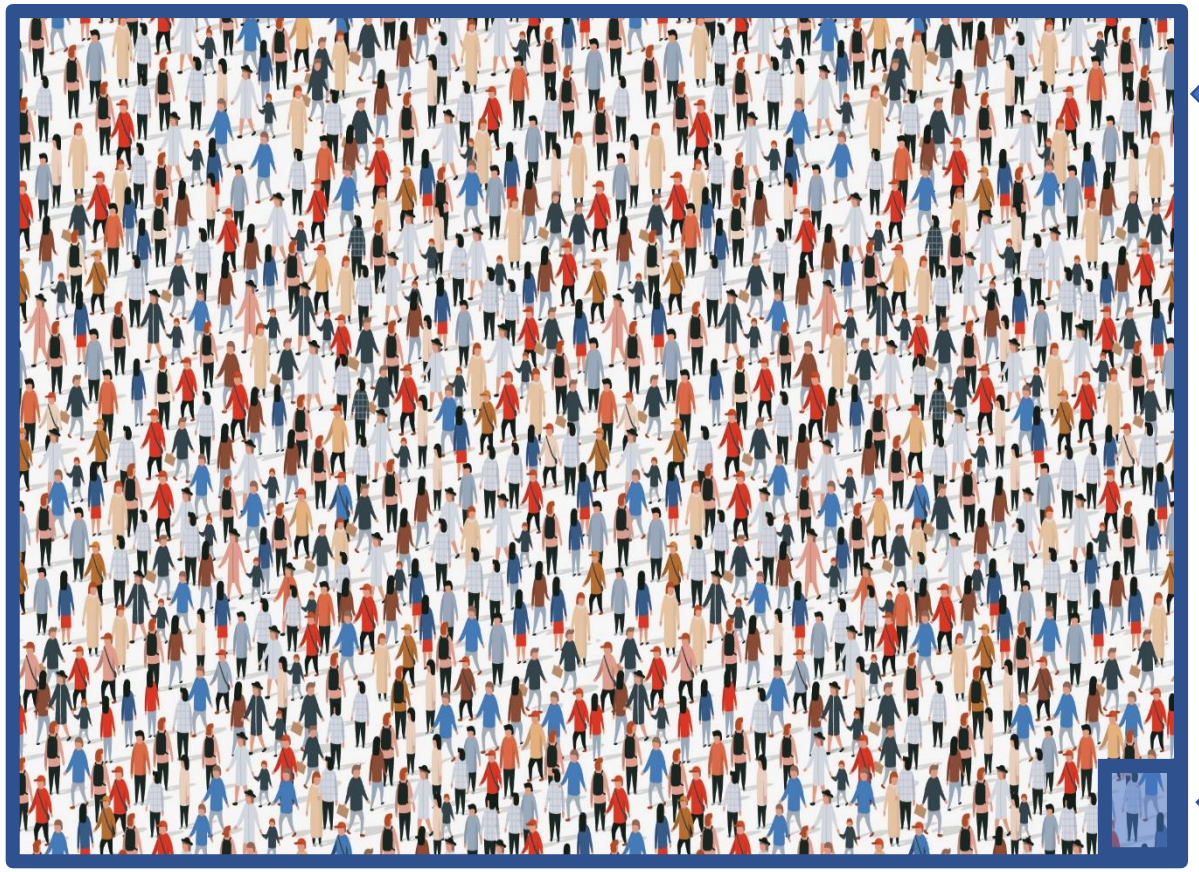
The ‘perfect’ CDD design overcomes two hurdles:

Small population
Regulatory approval

The CDD population is rare



Orphan drug designation
<200,000 (US)
0.05% (EMA)

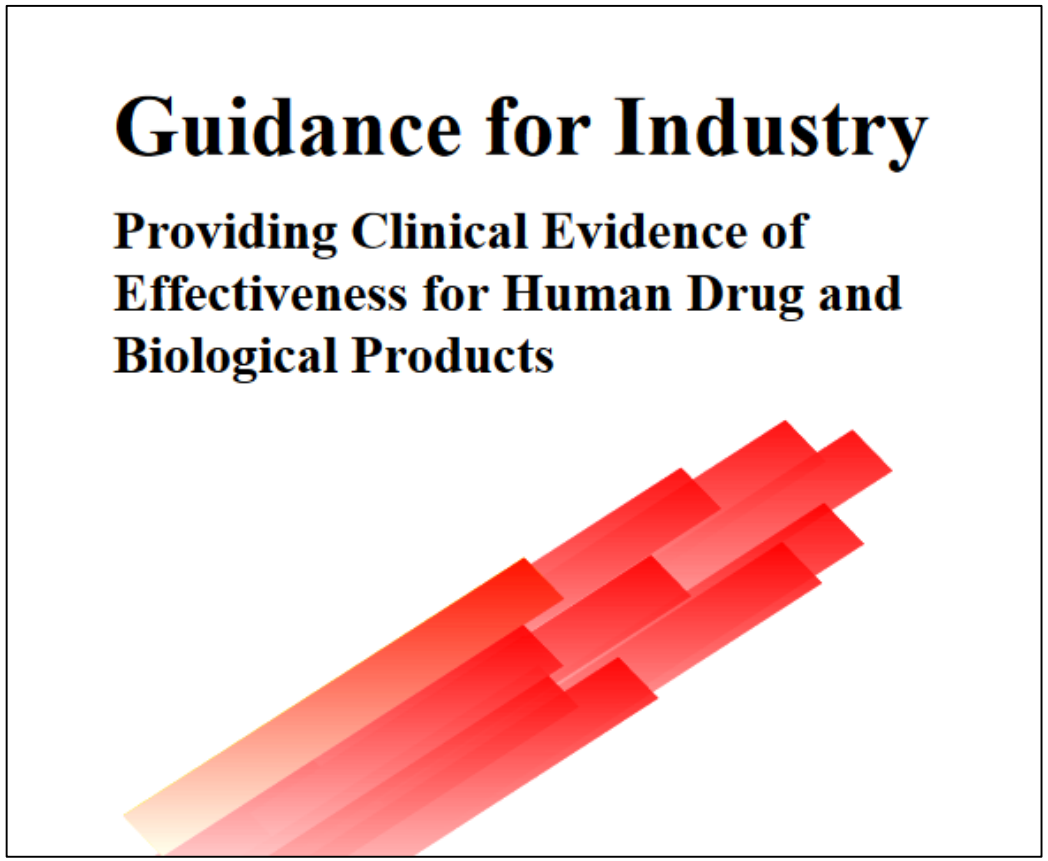
CDD world-wide
>1,000

Single study needs to support regulatory approval

Benefit

Risk

Reliance on a single study …



"**Leaves little room for study imperfection**"

appropriately designed
minimal possibility of bias
clear prior hypothesis

Source: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998. (https://www.fda.gov/media/71655/download)

How to show treatment is effective

FDA requires

- Substantial evidence
- Adequate and well-controlled study (or studies)

Substantial evidence must support effectiveness claim

"... **adequate and well-controlled investigations** provide the primary basis for determining whether there is **"substantial evidence"** ..."

"**Uncontrolled studies** or partially controlled studies **are not acceptable as the sole basis ...**"

Source: 21 CFR 314.126.

Two important adequate and well-controlled study (AWCS) characteristics…

Design permits a valid comparison with a control

Methods of assessment of subjects' response are well-defined and reliable

AWCS can use these 5 controls

- Placebo **concurrent** control
- Dose-comparison **concurrent** control
- No treatment **concurrent** control
- Active treatment **concurrent** control
- Historical control

Source: 21 CFR 314.126.

“Methods of assessment” are part of the endpoint pathway

What to consider when you select an instrument

Instrument appropriate for …

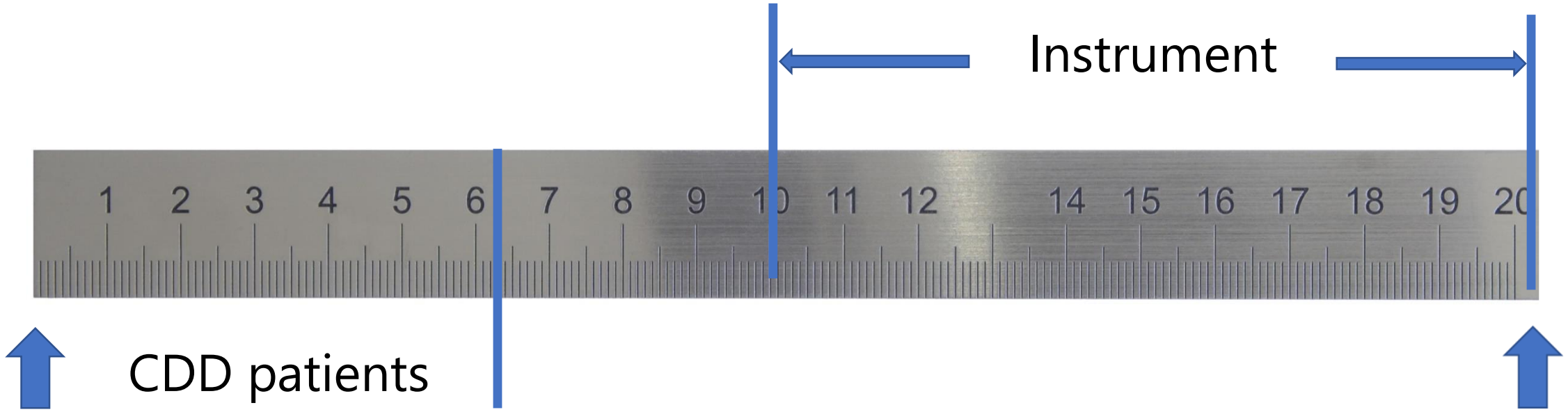
- CDD
- Severity
- Age

Key features to consider …

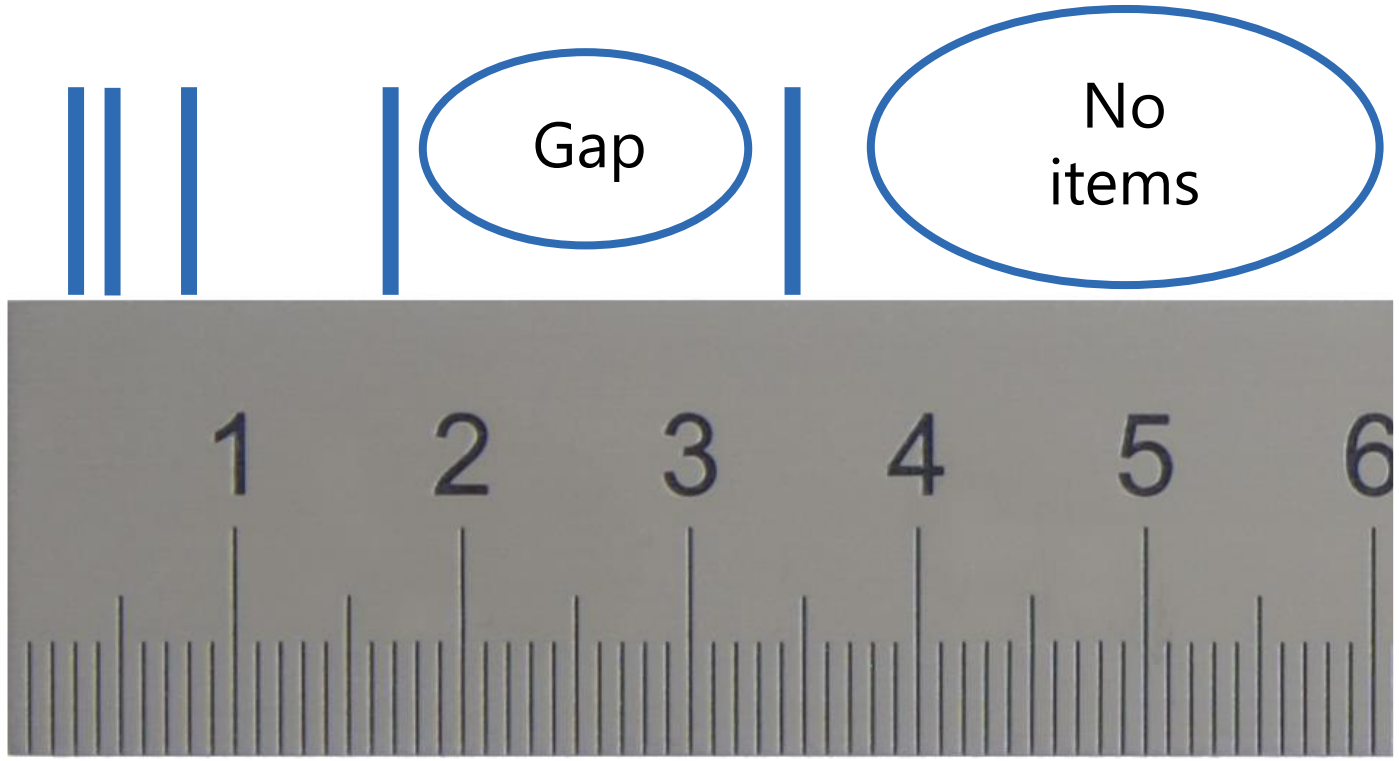
- Concepts
- Recall period
- Ability to detect change
  - Sensitive
  - Overlaps population
  - Child development
- Floor/ceiling effects

Ensure instrument targets study population

Does scale overlap population: ***No***



Ensure instrument targets study population



- Instrument (items) need to cover entire range
- May need to restrict study population

Can’t walk

Endpoints require a scientific question

- Common question: Is Treatment A more effective than Control?
- Needs more specificity
  - Population
  - Instrument
  - Endpoint
  - Intercurrent events
    - Start another treatment in addition to current treatment
    - Start another treatment, stop current treatment

A word on composite endpoints

- Can combine COA and non-COA endpoints
- The components are equally important
- Each component moves in the same direction

Example: Spinzara – Hammersmith Infant Neurological Examination-Section 2 (HINE-2))

- ≥2 pt increase (or max score 4) in ability to kick OR

  ≥1 pt increase certain movements (6 categories)
- AND improvement in more motor milestones than worsening

Design needs to align with scientific question

Spacing of assessments

- Align frequency and duration with scientific question
- Infrequent assessments may not estimate time of improvement.

Age range of patients

- Need to combine age-specific instrument assessments
- May need to limit age of patients in order to analyze

Enroll patients who can improve

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Sample size calculations require assumptions

- Prior to study start
  - Variance
  - Difference between treatments
- At interim analysis
  - Check assumptions
  - Upsize if necessary

Two upcoming meetings – live streamed

12 November 2019

ADEPT 6 Workshop: Pediatric Clinical Trial Endpoints for Rare Diseases

https://www.eventbrite.com/e/adept-6-workshop-pediatric-clinical-trial-endpoints-for-rare-diseases-registration-67523118465

6 December 2019:

Patient-Focused Drug Development: Guidance 4 – Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making

https://www.fda.gov/drugs/development-approval-process-drugs/public-workshop-patient-focused-drug-development-guidance-4-incorporating-clinical-outcome

Summary

- Get study design right the first time
- Regulatory approvals require
  - Adequate and well-controlled studies
  - Substantial evidence
- Use appropriate instruments and assessments
- The scientific question helps define the study endpoint
- Designing a study is difficult when limited information available for assumptions

References

FDA Guidance Documents:

- Draft Guidance for Industry, Rare Diseases: Common Issues in Drug Development, 2019. (https://www.fda.gov/media/119757/download)
- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998 (https://www.fda.gov/media/71655/download)
- Draft Adaptive Design Clinical Trials for Drugs and Biologics, 2018. (https://www.fda.gov/media/78495/download)
- Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, 2009. https://www.fda.gov/media/77832/download

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Definition of adequate and well-controlled studies
21 CFR 314.126: (https://www.ecfr.gov/cgi-bin/text-idx?SID=784ef3c18f0a3123c7ee637fd47aa4dc&mc=true&node=se21.5.314_1126&rgn=div8)

FDA's Complex Innovative Trial Design Pilot Program
(https://www.fda.gov/drugs/development-resources/complex-innovative-trial-designs-pilot-program)

Discussion Document for Patient-Focused Drug Development Public 2 Workshop on Guidance 3: 3 SELECT, DEVELOP OR MODIFY FIT-FOR-PURPOSE 4 CLINICAL OUTCOME ASSESSMENTS https://www.fda.gov/media/116277/download

Master protocols:
Janet Woodcock, M.D. and Lisa M. LaVange, Ph.D., "Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both", NEJM 2017. (https://www.nejm.org/doi/10.1056/NEJMra1510062)

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Rare disease publications

- Simon Day, et. al., “Recommendations for the design of small population clinical trials”, Orphanet Journal of Rare Diseases, 2018. (https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0931-2)
- Thomas Morel and Stefan J. Cano, “Measuring what matters to rare disease patients – reflections on the work by the IRDiRC taskforce on patient-centered outcome measures”, Orphanet Journal of Rare Diseases, 2017. (https://ojrd.biomedcentral.com/track/pdf/10.1186/s13023-017-0718-x)

Adaptive design examples for rare diseases

Miller, Eva, Paul Gallo, Weili He, Lisa A. Kammerman, Kenneth Koury, Jeff Maca, Qi Jiang et al. "DIA’s Adaptive Design Scientific Working Group (ADSWG) Best Practices Case Studies for “Less Well-understood” Adaptive Designs." Therapeutic innovation & regulatory science 51, no. 1 (2017): 77-88. (https://journals.sagepub.com/doi/pdf/10.1177/2168479016665434)

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Assessing Neurocognitive Outcomes in Inborn Errors of Metabolism

Food and Drug Administration, Proceedings of Meeting held on April 16, 2015. https://wayback.archive-it.org/7993/20170112081133/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM493766.pdfih.gov/pmc/articles/PMC4895194/

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Thank you!

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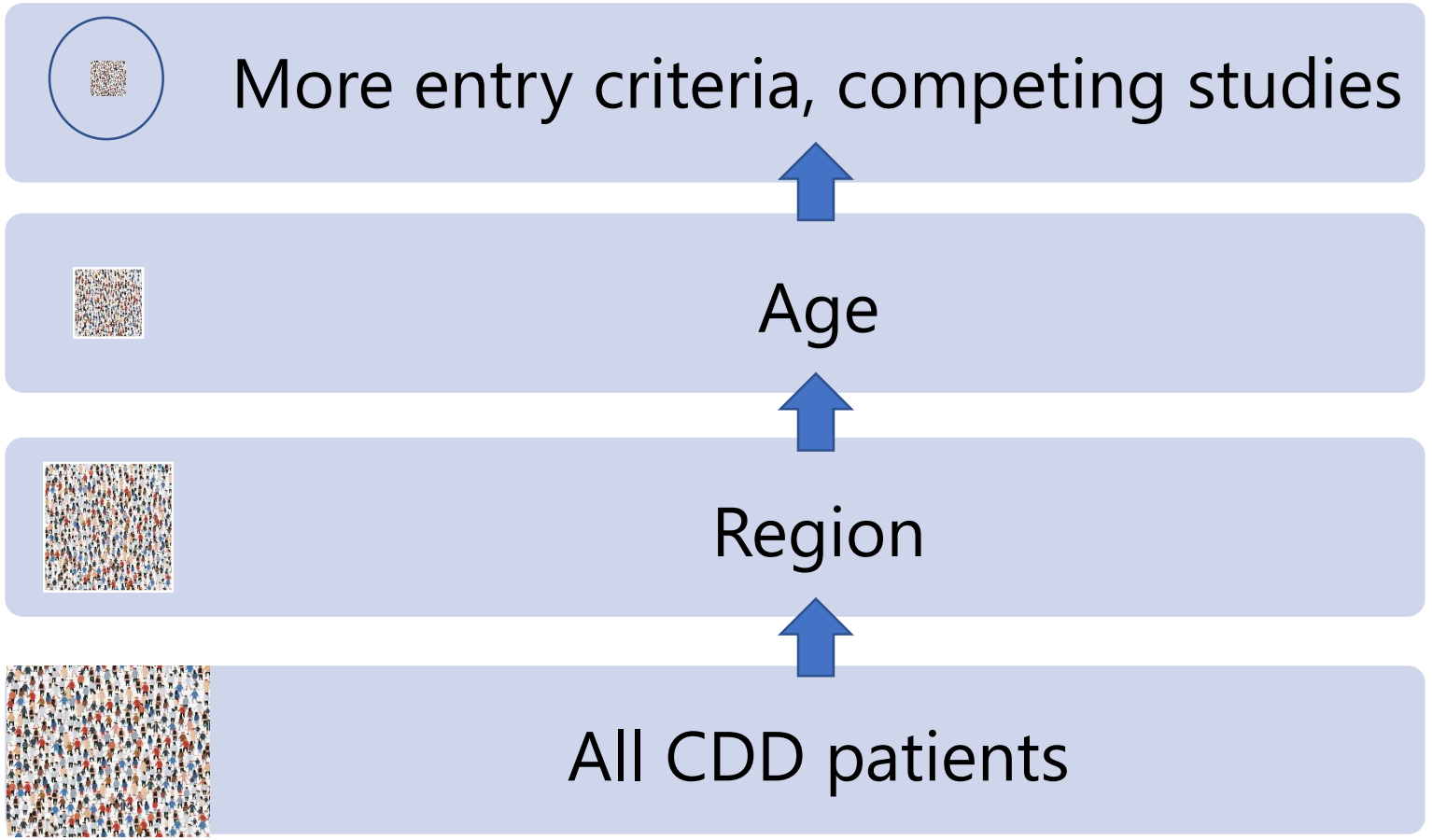
Bonus slides

Entry criteria and competing studies diminish the # of eligible patients



Scientific question → Patient-level endpoint

Between group difference in…	… then patient-level endpoint
Mean change from baseline to a specific visit	Change from baseline to a specific visit
Mean outcome at a specific visit	Outcome at a specific visit
Mean outcome at a set of specified visits (e.g., Visit 1, Visit 2, etc.)	Time profile (vector of outcomes at specific visits)
The area under the mean curves	Time profile (vector of outcomes at specific visits)

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Scientific question → Patient-level endpoint

Between group difference in…	… then patient-level endpoint
Proportion of responders	Responder (Yes/No) at a specific visit
Time-to-deterioration	Deteriorated (Yes/No) and time of response
Time-to-improvement	Improved (Yes/No) and time of response