Decentralised trials (DCT): Are we in control ?

Beyond operations, what are the scientific considerations ?

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Agenda

From the Covid-19 experience to deeper considerations

Driving the trial design: estimands

Proposed framework

Case study

- The research question & purpose of decentralization
- Thinking through the 5 attributes

Conclusion

From the COVID-19 experience…

The Covid-19 experience 

- Increase in trial activities conducted remotely and in participant's home, by necessity
- Development of regulatory guidelines :
  - Initially on the management of clinical trials during the COVID-19 pandemic
  - Focus shifting to the implementation of decentralised elements in clinical trials

The promises of decentralization 

- "Bringing the trial to the patients rather than the patients to the trial site"
  - Faster recruitment, reduced patient burden, better patient engagement and retention...
  - More inclusive or diverse trial populations, novel "real life" endpoints, enhanced patient experience...

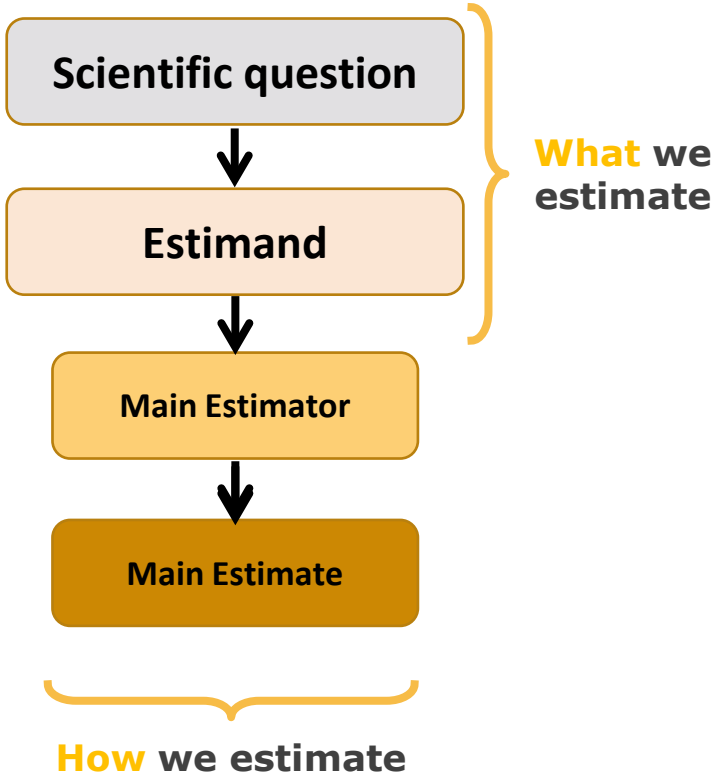
Sponsor's reactions (Mc Kinsey & Co, June 2021) 

- Develop a strategic approach to trial decentralization:
  - where does it help ?
  - What are the technical solutions, tools and capabilities to develop or acquire ?
  - How do we enable organizations to change ?

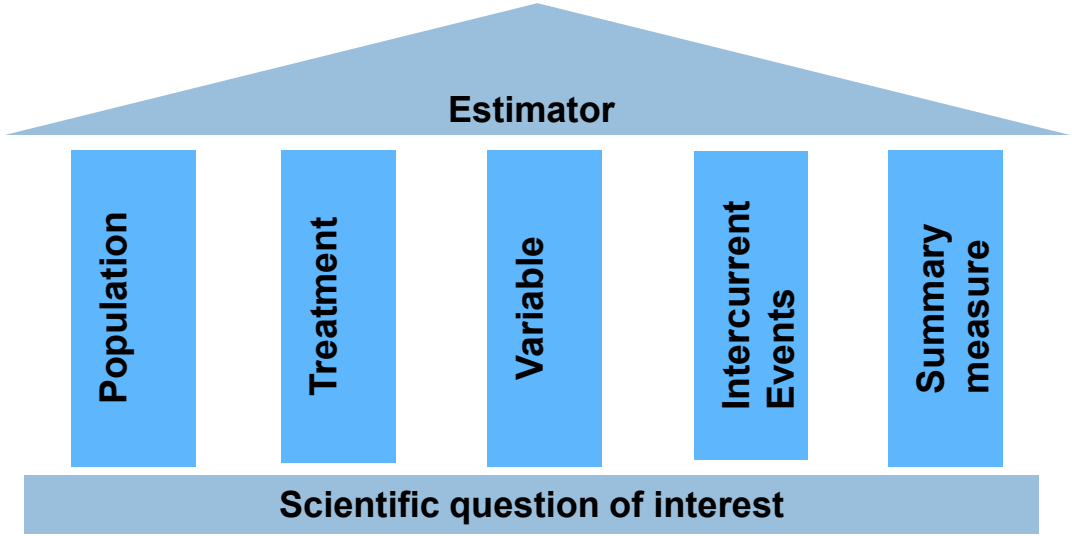
…to deeper considerations

- Increasing number of publications, reports, forums and web resources
- Enhanced access to devices, tools, platforms and technological solutions
- More regulatory questions and expectations
  - Dialogues and enquiries with sponsors (FDA OCE survey and request for data, Project SignifiCanT discussions, etc...)
  - Request for justification of DCT components
- More published design examples
  - “DCT Methodology studies”:
    - Validation of novel technology or endpoint, comparison of DCT vs. on site components
  - “Drug development studies”:
    - Fully decentralized or hybrid trials to assess a treatment effect
- Are we clear on what we do ?
  - Operational and technical aspects
  - What about scientific challenges and outcomes ?

Driving the trial design: estimands



- For any drug development study:
  - Scientific question -> define estimand attributes
  - Review patient journey -> identify intercurrent events
  - Estimand -> drives estimator & design characteristics



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Are we in control ? => Proposed framework

To maximize the value of decentralization :

- Think broad on **the research question**, and articulate **why decentralize**:
  - Is the purpose of decentralization driven by the question ?
  - Is the question taking full advantage of the opportunities of decentralization for broader, better, more relevant questions?

- Carefully review **planned DCT components**, and interrogate each **estimand attribute and the patient journey**:
  - Are they addressing the research question, how are DCT components accounted for ?

- Consider the resulting
  - WHAT: Are we clear on the question/estimand really addressed ?
  - HOW: Is the answer/estimate reliable ?

➢ **Refined estimand** or better understanding of the **estimator properties**

➢ Opportunities identified, assumptions clarified, scientific challenges addressed

Are we in control ? => Proposed framework

Research question
Estimand

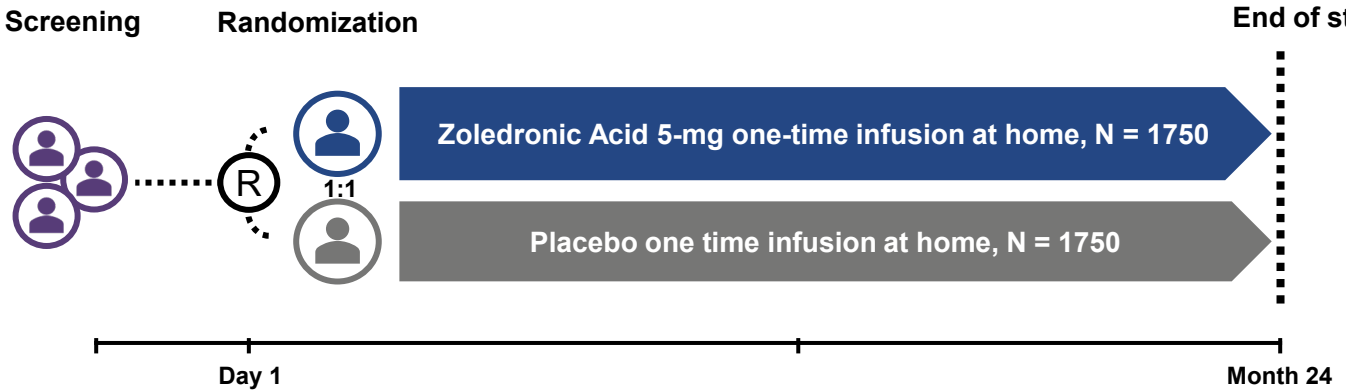
Why decentralize ?
DCT components

DCT components => need for more granular estimand attributes (WHAT) ?
- Is it possible that a different treatment effect is being estimated ?
- Does the DCT fit within the rest of the development plan ?
- Can an impact on label be expected ?

DCT components => need to better characterize the estimator (HOW) ?
- Is our estimator well characterized (variability, sensitivity, specificity...) ?
- Does the design account for actual estimator properties (e.g., sample size and power)
- Is the DCT design providing a reliable and externally valid answer to the question ?

Case Study: TOPAZ
("Trial Of Parkinson's And Zoledronic acid")

- US-wide, home-based, double-blind, Phase 4 trial
  single infusion of zoledronic acid vs. placebo to prevent fractures
  in men and women aged 65 years and older with neurodegenerative parkinsonism



Estimated study completion: **Feb 2026**

Remote follow-up by telephone, mail, email, medical record review
Outcomes: clinical fractures, hip fractures, mortality

npj Parkinson's Disease (2021)7:16 ; https://doi.org/10.1038/s41531-021-00162-1

https://clinicaltrials.gov/ct2/show/NCT03924414

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TOPAZ: Disease area problem statement

- Patients with Parkinson's Disease (PD)
  - have a high risk of fracture,
  - with likely greater risk of consequences - sustained disability and death
- Barriers to traditional treatment of people with PD:
  - conventional assessment **not familiar to neurologists** and **burdensome** for people with PD
    (Bone Mineral Density –BMD- testing and medical visits for interpretation, prescription of osteoporosis treatment, and follow-up to assess response to treatment).
  - **compliance with oral treatments for osteoporosis** notably poor.
    (even worse for older people with PD who are taking treatments for PD and other conditions).

TOPAZ : Research Questions

- TOPAZ aims to determine whether a treatment that improves BMD and reduces fractures in people with osteoporosis or hip fracture also reduces fracture risk in people with parkinsonism.

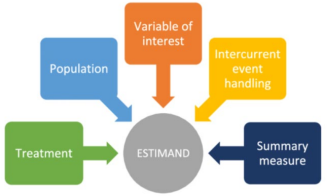
- It also tests a novel approach to treatment: that any person with parkinsonism age 65 or older without contraindications to treatment would receive treatment without referral for evaluations or BMD testing.

TOPAZ : Purpose of decentralization

- Decentralized trial participants:
  - not receiving care in a specialty clinic
  - enrolled, assessed and treated completely from home.
    (consent online, telemedicine visits to confirm the presence of PD, research nursing to conduct medical screening and give parenteral therapy in homes).
- Broad reach of fragile population
  (elderly PD population at higher risk of fractures)
  - opens participation to almost any person with neurodegenerative parkinsonism, unlimited by their location
- Optimized convenience of treatment and evaluation of treatment effect
  - Not involving neurologists for procedures they are not familiar
  - No BMD testing, no site visits needed
- Better reflect future clinical implementation of study results

➢ Purpose of decentralization fully aligned and supporting research question

Population Attribute



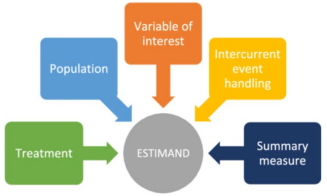
WHAT	HOW
Indication: new or modified by DCT components ? Any difference with indication targeted by other trials in the development plan ?	**Selection bias** : any over/under-representation of some patients induced by DCT procedures ?
Subgroups: any subgroup affected by DCT components, with potential different treatment effect ? Any expected difference with subgroups of importance in the rest of the development plan ?	**Sample heterogeneity**: affected by DCT ?
Patient diversity and treatment mode of action: any unknown on possible sensitivity factors, interactions ?	**Patient diversity characterization**: ability to ascertain eligibility, identify subgroups, etc... Affected by DCT ?
	Population inclusiveness: higher external validity ?

TOPAZ : 5-attributes Discussion

Population

- Participation within the US is not restricted by site proximity and recruitment is done from many sources
- More disabled and cognitively impaired patients – who may benefit most
- No BMD testing prior to treatment – which is usually the case
  - HORIZON trial data: efficacy of zoledronic acid for fracture risk reduction found similar regardless of a person's BMD. Confirmed by randomized trial of zoledronic acid in older women with *T*-score above −2.5 (Reid, 2018).
  - Consent process emphasizes that potential participants may opt to have BMD testing and seek evaluation and treatment instead of participating in the trial.
- Unique indication in broader population enabled by decentralization
  Possible challenges in characterizing the population (e.g. BMD, diversity of referral routes and documentation of characteristics, etc...)

Treatment Attribute

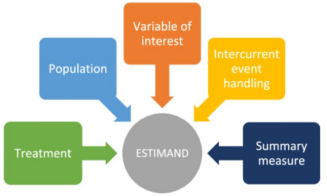


WHAT	HOW
Interventions, schedule and mode of administration: new or modified by DCT components ? Any relevant difference with definition of treatment in other trials in the development plan or in the disease area?	**Variability in compliance** : any expected change induced by DCT setting and procedures ?
Patient diversity and treatment mode of action: any unknown on possible sensitivity factors, interactions ?	**Homogeneity of Treatment procedures**: any procedure likely to differ across the diversity of administration settings and of population ? Can patient management be defined and followed as planned ? Can treatment assignment be stratified by the relevant factors and in line with the rest of the development plan or in the disease area?
	Assessment of patient management and ascertainment of treatment procedures and exposure: ability to ascertain compliance, protocol deviations, etc... affected by DCT ?

TOPAZ : 5-attributes Discussion
Treatment

- Is this the same “treatment” as studied in other trials/as labelled ?
  - Tailored infusion protocol to minimize risk of ‘acute phase reaction’
  - no BMD testing, site visits, etc...
- All patients having at home treatment with single infusion by nurse
  - Limited risk of interaction between higher patient diversity (from broad recruitment and absence of BMD testing) and treatment mode of action, as partly supported by data
  - Controlled compliance
  - Limited risks of heterogeneity of treatment procedures and patient management

Variable
Summary measure Attributes



WHAT	HOW
Variable relevance: Any impact on fitness for purpose, accuracy, sensitivity, specificity, validity, relation to clinical benefit of DCT instrument, device, mode and setting of measurement, and overall procedures ? Any ambiguity in the definition of the variable ? Any expected challenge to comparability with measurements in other trials in the development plan ? Any expected challenge to comparability with established measurements in the field ? What evidence is available to support those, including for regulatory stakeholders ?	**Variable operating characteristics**: any impact on variability, reliability, correlations induced by DCT instruments, mode and setting of measurement, and overall procedures ? Ability to stratify the summary measure by relevant factors affected by DCT ?
	Frequency of measurement, missing data mechanisms: affected by DCT procedures ?
	Ascertainment of quality, accuracy, reproducibility, etc... Of measurements: any issue introduced by DCT setting ?
Unexpected confounders: any interactions or confounders possibly introduced by DCT components ?	**"Real life" setting**: higher external validity ? How is the proximity to "real life" assessed and ensured ?

TOPAZ : 5-attributes Discussion

Variable: time to first clinical fracture

- Trial participants or their proxies **contacted by Coordinating Center** every 4 months by postcard, telephone, or email, **about occurrence of fracture or falls** during that interval.
  - Report of a fracture => collection of data about date and location of medical care to **obtain objective documentation** of the fracture in a radiology report or discharge summary
- For participants who originated **from health systems,** the system performs an annual **search of the EHRs** for diagnoses of fracture or occurrence of death, along with collection of X-ray reports or discharge summaries confirming the event.
- Definition and required evidence different from previous studies, expected different properties (impact on design ?)
- Any impact on typical method to account for missing data?
- Comparisons between the home and office measures: is variability/treatment effect, the same? How to interpret potential differences between this trial and other trial results?

TOPAZ : 5-attributes Discussion
Variable (cont'd)

- HORIZON trial (zol acid Ph3 trial):

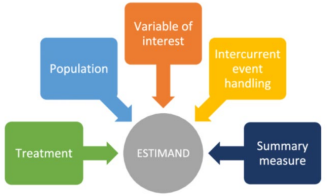
Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

Dennis M. Black, Ph.D., Pierre D. Delmas, M.D., Ph.D., Richard Eastell, M.D., Ian R. Reid, M.D., Steven Boonen, M.D., Ph.D., Jane A. Cauley, Dr.P.H., Felicia Cosman, M.D., Péter Lakatos, M.D., Ph.D., Ping Chung Leung, M.D., Zulema Man, M.D., Carlos Mautalen, M.D., Peter Mesenbrink, Ph.D., Huilin Hu, Ph.D., John Caminis, M.D., Karen Tong, B.S., Theresa Rosario-Jansen, Ph.D., Joel Krasnow, M.D., Trisha F. Hue, M.P.H., Deborah Sellmeyer, M.D., Erik Fink Eriksen, M.D., D.M.Sc., and Steven R. Cummings, M.D., for the HORIZON Pivotal Fracture Trial*

Clinical fracture reports were obtained from patients at each contact. Nonvertebral fracture reports required central confirmation, which was performed at the UCSF Coordinating Center. Evidence included either a radiologic or surgical procedure report or a copy of the radiograph. Excluded were fractures of the toe, facial bone, and finger and those caused by excessive trauma (assessed centrally as sufficient to cause fracture in a person without osteoporosis[2]). For clinical vertebral fractures, the community-obtained radiograph was compared with the baseline study radiograph by a central reader at Synarc, and semiquantitative confirmation was required.

Dual-energy x-ray absorptiometry of the hip was performed at baseline and at months 6, 12, 24,

Intercurrent Events Attribute



WHAT	HOW
New Intercurrent events related to DCT (Home) setting or to devices and instruments	**Ability to report intercurrent event occurrence:** affected by DCT setting, e.g., use of EHR or a diversity of data sources ?
Change in frequency of usual intercurrent events	**Higher variability of intercurrent event impact on estimate:** affected by diverse DCT setting ?
Ability to anticipate and pre-specify important intercurrent events**:** affected by diversity and lower control on DCT setting ?	**Reliability of characterization of intercurrent events** (root cause, dates, context...) **:** affected by DCT setting ?
Ability to assess clinical relevance of intercurrent events**:** affected by variability and lower control on DCT setting ?	**"Real life" setting**: higher external validity of a "treatment policy" approach to intercurrent events ? How is the proximity to "real life" assessed and ensured ?

TOPAZ Study: 5-attributes Discussion
Intercurrent (I/C) Events

- Is decentralization impacting any of the I/C events typically used for primary estimand definition? For example:
  - Any other I/C event that could result from doing home visits rather than office ones?
  - Any I/C event no longer to be considered in home setting vs. traditional setting ?
  - Different study dropout rate to be expected ?
  - Any specific concomitant medication intake or dosing adaptation that would be different from home vs office administration ?
- Access to the root causes of I/C events for mitigation or interpretability purposes?
- Altered reporting rates of identified I/C events?

Conclusion

- Estimand framework facilitates careful thought process needed in DCT
- Question on estimand vs. estimator affected by DCT setting ?
  - Depends on the granularity of the estimand definition
  - To be driven by the particular stakeholder focus, the drug development context, the mode of action, disease setting, other identified causal factors
- Clarity needed early on regarding opportunities, assumptions, challenges
  - Development plan and study design implications
  - Regulatory consultations
  - Need to validate assumptions with “DCT Methodology studies” ?
- Additional challenges with hybrid designs, and with “DCT Methodology studies”
  - Low hanging fruit operationally may be more challenging scientifically
  - Low risk vs. High reward trade off:
    favoring trials where full DCT setting is essential to the research question ?

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Thank you

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Back up

Flow of Participation in TOPAZ Study

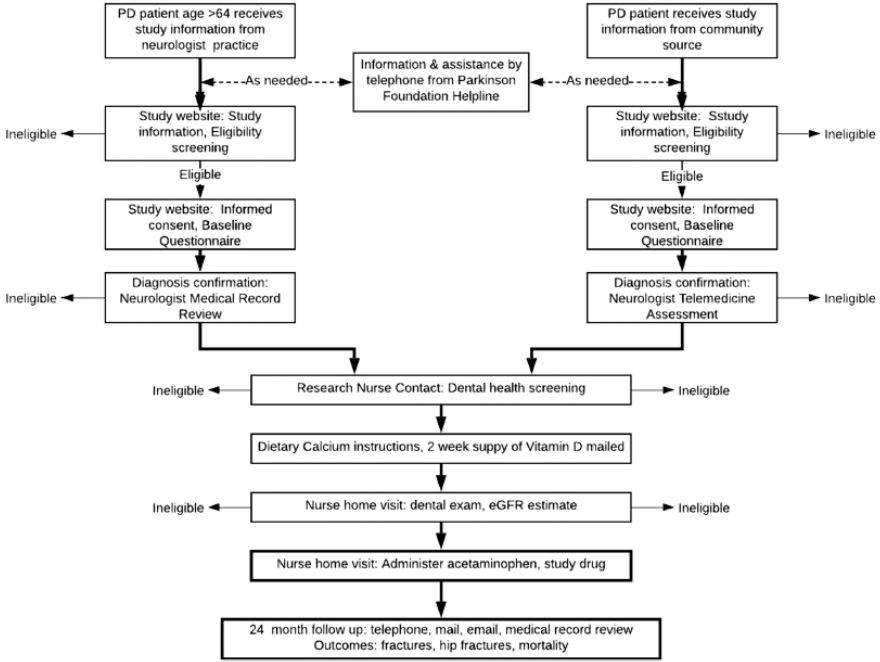

Fig. 2 Flow of Participation in TOPAZ Study. Participants may self-refer or be referred by neurologists. Informed consent is provided online and treatment is provided in the home. Followup isconducted remotely.

npj Parkinson's Disease (2021)7:16 ; https://doi.org/10.1038/s41531-021-00162-1

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TOPAZ: 3 interactions with Participants

- initial eConsent and eligibility screens collected online
- a teleneurology examination conducted to confirm the diagnosis of Parkinson's disease
- a nurse to administer a finger stick at the participant's home to assess kidney function, then provide either zoledronic acid or placebo

npj Parkinson's Disease (2021)7:16 ; https://doi.org/10.1038/s41531-021-00162-1

TOPAZ: Exclusion Criteria

- History of hip fracture
- Any use of a bisphosphonate drug within the last 12 months
- Use of any other osteoporosis treatment (such as SERMs and denosumab) within the last 6 months
- Tooth extraction or invasive dental procedures within the past 30 days or planned/scheduled extraction/procedure in the next 12 months
- Non-ambulatory, i.e., unable to walk without assistance of another person.
- Undergoing kidney dialysis
- A diagnosis of multiple myeloma or Paget's disease
- Unable to speak or read English sufficiently to complete informed consent
- Any other criteria, which would make the patient unsuitable to participate in this study as determined by the study staff (e.g., an uncontrolled drug and/or alcohol addiction)

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TOPAZ Study: Sample Size

Sample size

TOPAZ will be the largest double-blind placebo-controlled randomized clinical trial ever conducted in people with parkinsonism. TOPAZ plans to enroll 3500 participants who are age 65 years or older. Each of the endpoints will be analyzed using Cox proportional hazards regression. This number of participants will provide the trial 90% power to detect a 25% reduction in the risk of any fracture, a clinically important reduction that is similar to the approximately 30% reductions seen in osteoporosis trials[9,23]. Power will be 80% to detect the secondary end point of a 40% reduction in hip fracture and the exploratory end point of a 28% reduction in mortality.

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