Concept for evaluation of remote endpoint assessment by integration of an orthogonal crossover equivalence sub-study within longitudinal parallel trial designs

James Bell – Elderbrook Solutions GmbH

13rd September 2021

Remote Assessment Equivalence

Introduction

- COVID-19 has caused much trial conduct disruption
  - Not always possible to get patients to sites
- Remote endpoint assessment was a possible *ad hoc* solution
- But is it equivalent to in-person assessment?
  - Particularly pertinent for Patient Reported Outcomes (PROs) and rated assessments
- Decentralized trials targeting same endpoints as 'standard' trials face similar issues
  - Need evidence that systematic remote endpoint collection is equivalent
- This talk proposes a design to demonstrate equivalence within existing trial envelope

Remote Assessment Equivalence — Why Different?

- Endpoints often only validated under specific administration setting
  - Have to show remote assessment is equivalent

- Remote assessment may be different because of:
  - Different questionnaire administration (e.g. online *vs* paper, oral *vs* written)
  - Different interview conditions (in-person *vs* video *vs* phone)
    - Well-known differences in inter-personal interactions depending on media
    - Change in ease of assessing oral and visual clues
  - Different setting (home vs on-site)

Remote Assessment Equivalence — Setting

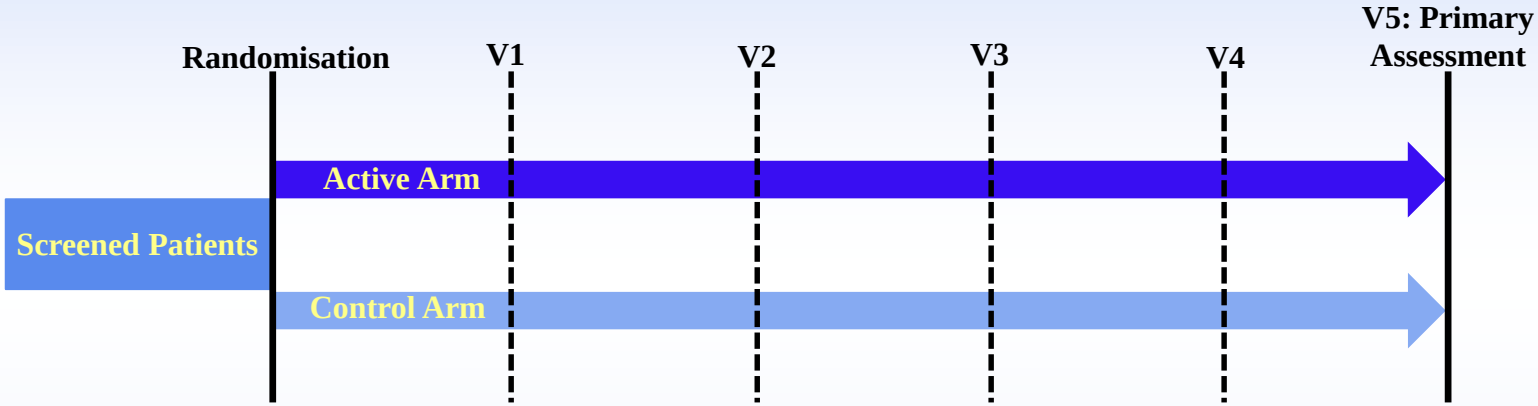
- **PRO or assessor-based outcomes,** continuous / discrete longitudinal measurements
  - E.g. KCCQ (heart failure), ZAN-BPD (borderline personality disorder)

- Main setting of interest:
  - **Ph II trial ahead of fully decentralised Phase III trial(s) targeting 'on-site estimand'**
    - Want to demonstrate endpoint equivalence in advance
    - Validates remote assessment and increases acceptance for future phase III

- Also consider a secondary setting:
  - **Phase III trials with mixture of on-site and remote endpoint collection**
    - Want to demonstrate equivalence/interchangeability, or adjust if not
    - Have to be wary of outcome affecting method of assessment

Remote Assessment Equivalence

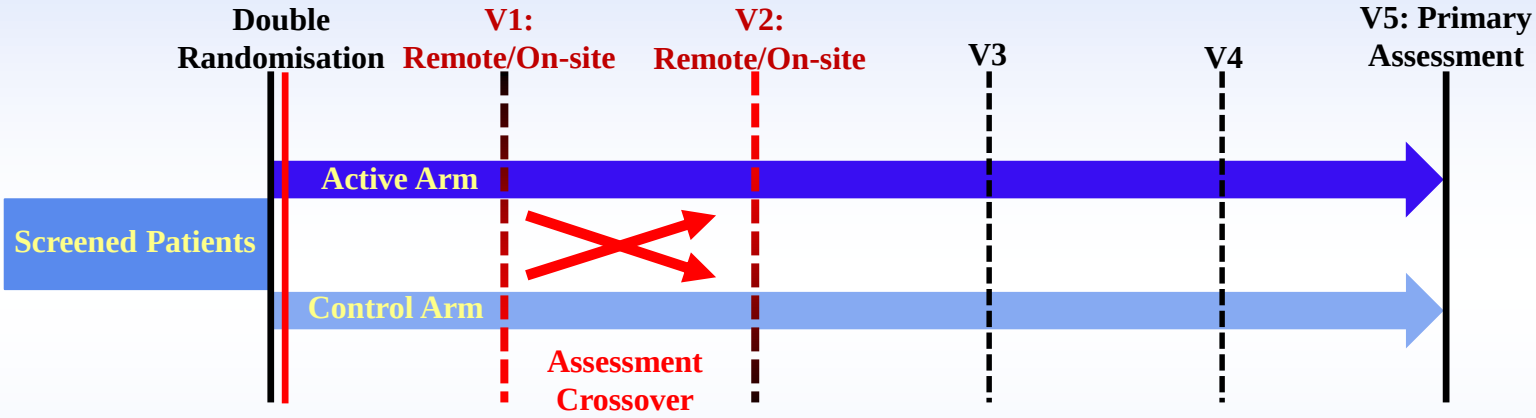
Standard Design



- Standard 5 on-site visits parallel, randomised, double-blind, longitudinal design
- Continuous/discrete measurements at each
- Primary endpoint is at final visit
- MMRM (or similar) analysis
  - V1-4 measurements used primarily to address missing data at V5
    - Inefficient use of data

Remote Assessment Equivalence

Proposed Design



- Still 5 visits parallel, randomised, double-blind, longitudinal design
- Patients additionally randomised to orthogonal 2x2 crossover design of assessment type:
  - One remote visit per patient, which one determined by second randomisation
    - E.g. patients randomised to remote assessment at either visit 1 or visit 2
    - Use of early & adjacent visits preferable
- Later visits (incl. primary assessment) unaffected

Remote Assessment Equivalence — Analysis

- Analysis by **MMRM with time-dependent covariate** (TDC) for assessment in model
  - Double-randomisation avoids standard problem of TDC correlation with trt

```
PROC MIXED DATA=input;
  CLASS subjid visit remote trt;
  MODEL result = trt*visit remote baseline*visit/ S DDFM = kr;
  REPEATED visit / TYPE = UN SUBJECT= subjid R;
  LSMEANS trt*visit /diffs;
  LSMEANS remote /diffs;
RUN;
```

- Standard 2x2 crossover model for *remote* on top of standard MMRM for *trt*visit*
  - Provides analysis of both efficacy and remote assessment
  - *remote* interactions with *trt* or *visit* could be considered for sensitivity analysis (only)
    - Assessment is orthogonal, and blinded, to treatment
    - Assessment should be independent of visit, transferable to other visits
- Test equivalence using standard margin-based approaches

Remote Assessment Equivalence

Advantages

- **No additional trial required to compare assessment types**
  - Fast, seamless and extremely efficient
- **Precise**: Larger sample sizes than standard crossover equivalence trial
- Randomised crossover allows intra-patient comparisons, distinguishes from *visit* and *trt* effects
  - Carry-over effects very unlikely as assessment is not a ‘treatment’
- Equivalence conditions in ‘efficacy’ setting; more relevant, less risk of assessor bias
- **Negligible impact on primary outcome**
  - Does not affect primary assessment visit
  - Affected visits used for missing data handling; still able to with effect adjustment
- Same approach useful in phase III to correct for mixed assessment practices
  - Randomised remote assessment removes/reduces bias from outcome-assessment correlations

Remote Assessment Equivalence — Limitations

- **Design not yet been tested in trial**
- **Some additional trial complexity**
  - Additional IRT randomisation
- Assumes constant, additive effect for assessment effect
  - Multiplicative effects, heteroscedastic effects etc not covered
  - However… in phase II post-hoc assessments still possible if important deviation
  - Also no different than in any other equivalence setting
- May have impact on estimation at visits directly involved, but…
  - Minimal if remote assessment effect is constant & additive
  - Assessment method is independent of treatment
- Assessment type must be adhered to rigorously to avoid introduction of bias

Remote Assessment Equivalence

Conclusions

- **Remote endpoint assessment may be different to in-person assessment**
  - Problem for relevance of decentralized trials
- **An orthogonal randomised crossover equivalence design may be seamlessly integrated into standard longitudinal efficacy trials**
  - Makes use of inefficiencies in standard longitudinal designs
- **Analysis *via* MMRM with time-dependent covariate in model**
  - Randomisation ensures independence of TDC from treatment
- **High precision, highly relevant and avoids need for additional trial**
- **Trial design still needs to be tested in real world**

Acknowledgements

- Acknowledgements to Boehringer Ingelheim for the ongoing collaboration
  - In particular, thank you to Jan Wruck for discussions on this topic