Please see below for a link to the webinar recording for the Trials Methodology Research Partnership:

The Implications of COVID-19 for Clinical Trials

Prof. Amanda Farrin, University of Leeds and Dr. Cornelia Ursula Kunz, Boehringer Ingelheim

24 June 2020

The slides and a copy of the questions submitted during the webinar are also available below.

For any queries, please contact uktmn@nottingham.ac.uk

https://www.youtube.com/watch?v=XrBcos1_oUg&feature=youtu.be

Implications of COVID-19 for clinical trials

TMRP Webinar: 24 June 2020

Amanda Farrin, University of Leeds

Cornelia Ursula Kunz, Boehringer Ingelheim

Webinar structure

Brief introduction to webinar – Amanda

Summary from CTU survey

Clinical Trials impacted by the COVID pandemic: Adaptive designs to the rescue? – Cornelia

Should we restart our paused trial? Deliberations and reflections from a case study – Amanda

Questions

CTU Survey

For randomised trials, which are not nationally prioritised COVID-19 studies and where recruitment has been paused,

Q1) have you been asked about, or have you considered not restarting?

11/31 responders considering not re-starting at least one trial.

CTU Survey Q2: Rationale for considering not restarting?

Proportion of target sample size recruited / Impact on power
How well recruiting previously
Level of follow-up/missing data
Trial design – cRCT issues
For feasibility studies: Can objectives be demonstrated with data so far

Significant impact on overall timelines / lengthy waiting time
Time critical outputs / Changing equipoise

Trial conduct difficulties post-suspension - social distancing / restrictions – for sites, researchers, patients
How long before NHS services able to get back to research;
Level of site input required (routine & light touch or not)
Disrupted treatment delivery / compliance / is intervention still relevant?

Funding / cost issues

DMC recommendation

CTU Survey Q3: If restart decision based on analysis of available data, what statistical approaches considered?

Review **power calculations** (if stopping early)

Review available data for primary analysis

Review sample size assumptions (given actual data)

Assess conditional power

Maximise power

- Incorporate correlation between baseline and follow-up
- Extend follow-up to observe a higher event rate
- Consider alternative analysis methods – time to event

Review analysis plans - Missing data / MI, additional CACE analyses.

Consider prospective meta-analysis

Consider interim analysis with stopping rules for efficacy/futility

Recruitment – estimated how long to reach target, some assuming same pre-COVID rates; assessing need for costed/uncosted extension

Clinical trials impacted by the COVID-19 pandemic: Adaptive designs to the rescue?

Cornelia Ursula Kunz
(on behalf of the working group)

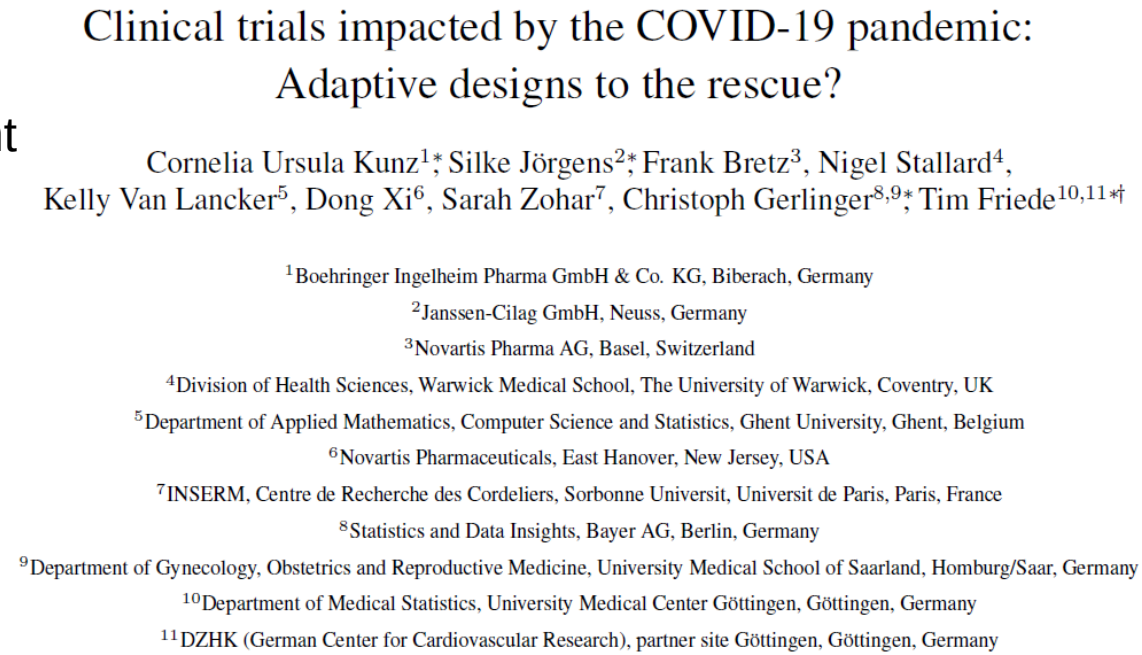
IBS-DR German Region: Adaptive Designs Working Group

- Call for volunteers for a paper on adaptive trial designs for vaccines/treatments for COVID-19
- Decision to have two papers:
  – Paper on adaptive designs for vaccines/treatment for COVID-19
  – Paper on adaptive designs for trials affected by COVID-19

- Working group for paper 2:
  Core team:
  – Tim Friede (Univ. Göttingen),
  – Christoph Gerlinger (Bayer),
  – Silke Jörgens (Janssen),
  – Cornelia Ursula Kunz (Boehringer Ingelheim)
  In addition: Frank Bretz (Novartis), Nigel Stallard (Univ. Warwick), Kelly van Lancker (Univ. Ghent), Dong Xi (Novartis), Sarah Zohar (Univ. Paris)

Submitted Friday, 22 May 2020

(1) Introduction
(2) Motivating examples
(3) How adaptive designs might be used to overcome COVID-19 challenges
(4) Resizing the trial
(5) Regulatory and operational aspects
(6) Discussion



Clinical trials impacted by the COVID-19 pandemic: Adaptive designs to the rescue?

Cornelia Ursula Kunz[1]*, Silke Jörgens[2]*, Frank Bretz[3], Nigel Stallard[4], Kelly Van Lancker[5], Dong Xi[6], Sarah Zohar[7], Christoph Gerlinger[8,9]*, Tim Friede[10,11]*†

[1]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
[2]Janssen-Cilag GmbH, Neuss, Germany
[3]Novartis Pharma AG, Basel, Switzerland
[4]Division of Health Sciences, Warwick Medical School, The University of Warwick, Coventry, UK
[5]Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium
[6]Novartis Pharmaceuticals, East Hanover, New Jersey, USA
[7]INSERM, Centre de Recherche des Cordeliers, Sorbonne Universit, Universit de Paris, Paris, France
[8]Statistics and Data Insights, Bayer AG, Berlin, Germany
[9]Department of Gynecology, Obstetrics and Reproductive Medicine, University Medical School of Saarland, Homburg/Saar, Germany
[10]Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany
[11]DZHK (German Center for Cardiovascular Research), partner site Göttingen, Göttingen, Germany

Available on https://arxiv.org/abs/2005.13979

3 How adaptive designs might be used to overcome COVID-19 challenges

3.1 Where adaptations based on blinded data can help

Adaptations can be based on baseline patient characteristics; premature study or treatment discontinuations; missing data during follow-up; protocol violations; and nuisance parameters of the outcomes including event rates and variances

3.3 Treatment-effect heterogeneity

Combination of data collected pre and post outbreak might not always be possible. Case-to-case decision.

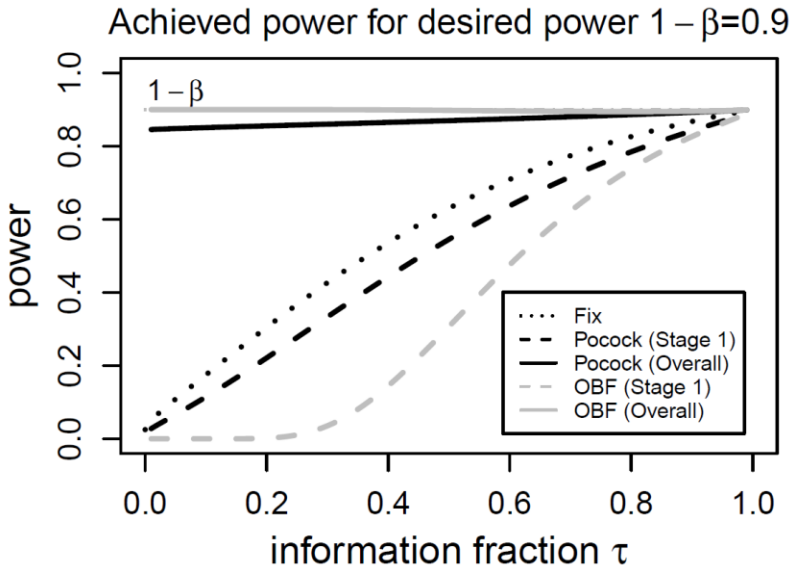
3.4 Use of early read-outs

Several methods exists allowing adaptations based on short-term endpoints.

4 Resizing the trial

4.1 Almost done: To stop or not to stop early

		$1-\beta = 0.90$			
		Pocock		OBF*	
		Stage		Stage	
τ	fix	1	2	1	2
0.50	0.630	0.545	0.870	0.307	0.898
0.60	0.709	0.637	0.875	0.476	0.896
0.70	0.774	0.717	0.880	0.622	0.895
0.80	0.826	0.785	0.886	0.739	0.895
0.85	0.848	0.815	0.889	0.786	0.895
0.90	0.868	0.842	0.892	0.826	0.896
0.95	0.885	0.868	0.896	0.862	0.897
0.99	0.897	0.890	0.899	0.889	0.899

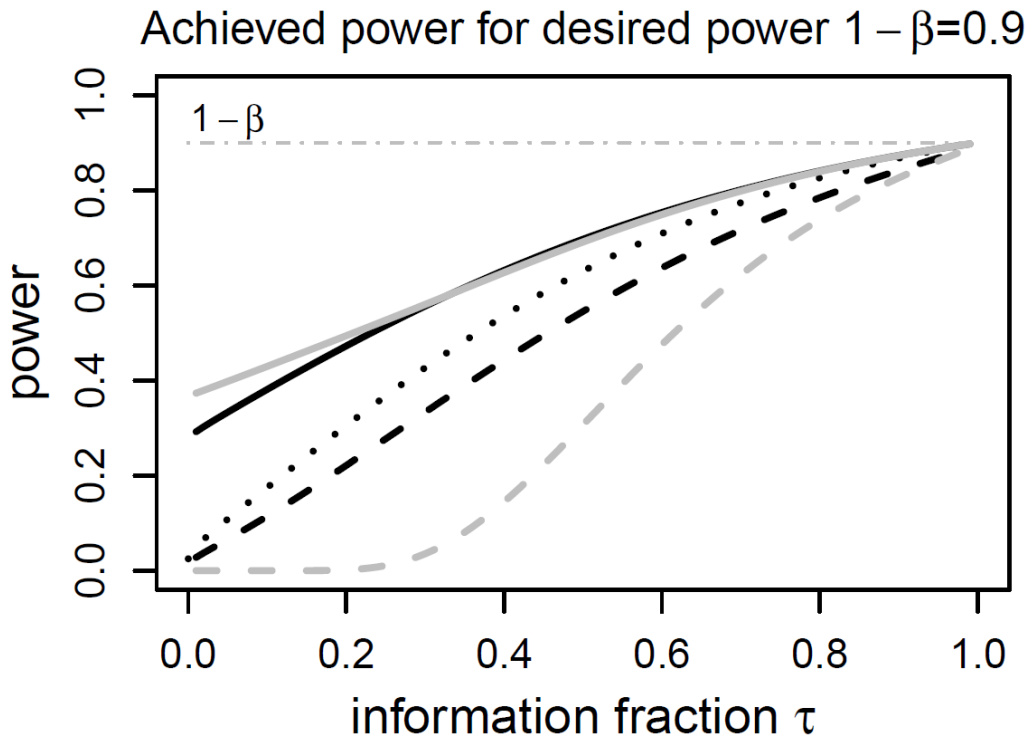


If approx. 85% of data is already available, the loss in power is approx. 5% points. Might as well stop trial now and analyze.

4.4 Dilution effect η (here, $\eta = 0.50$)

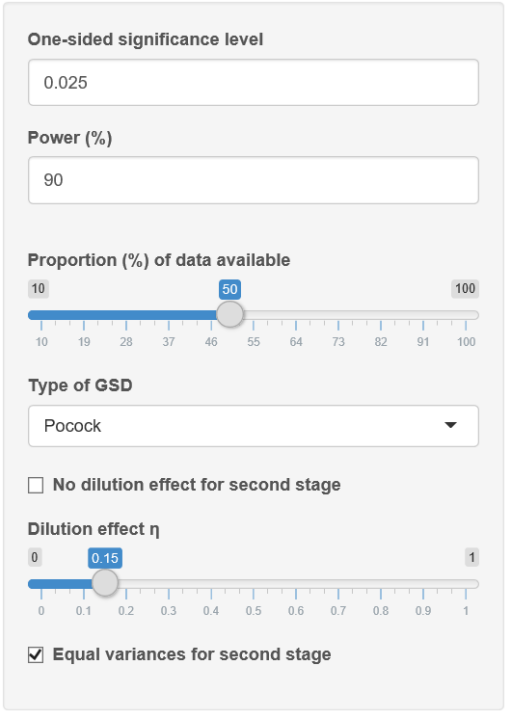
- Change of treatment effect and/or change of variance due to COVID-19

If the treatment effect and/or the variance changes after the outbreak, the power of the trial will decrease.



4.5 Sample size adjustment

- Adjust sample size for GSD due to multiple testing and/or to account for dilution effect



Achieved Power | Sample Size Adjustment

The trial was originally planned as an one-stage design with a fixed sample size for the following parameters:

Treatment effect δ	Standard deviation σ	Randomization ratio 1:r (plc:trt)
0.5	1	1

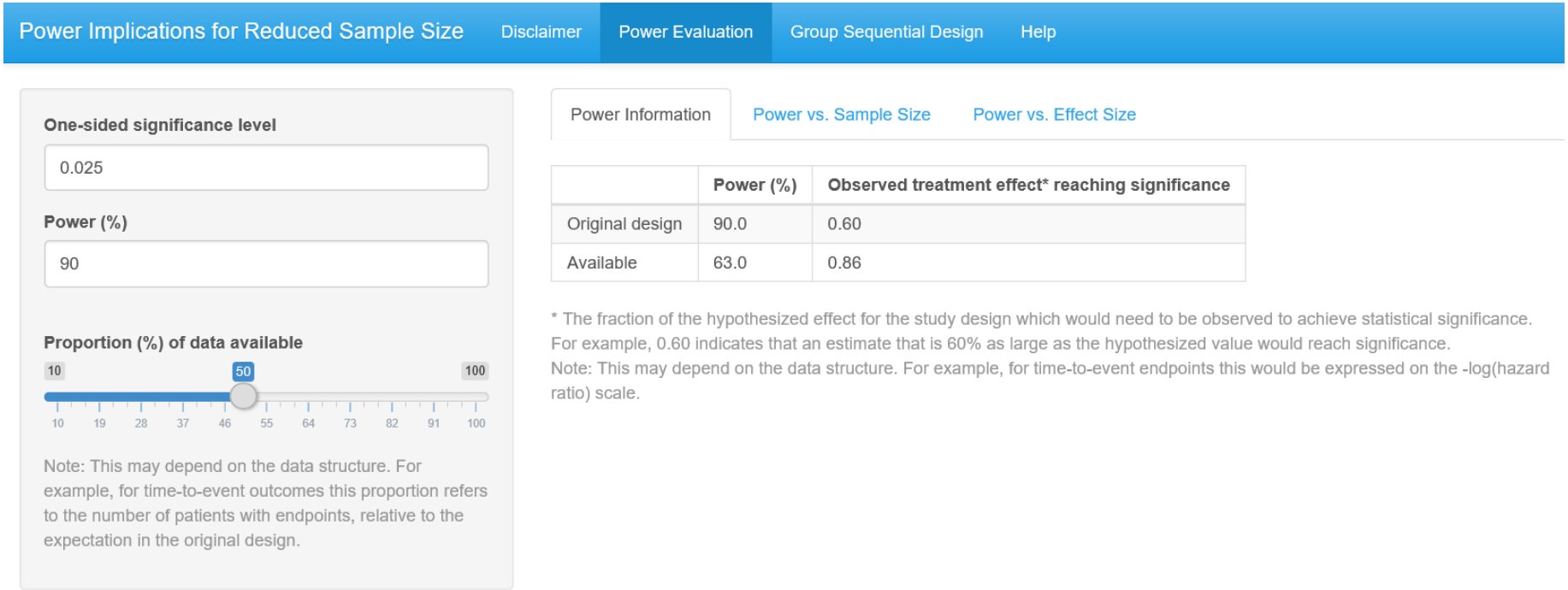
The originally planned fixed sample size was $N = 169$.

Assuming a dilution effect of $\eta = 0.15$ and a variance in-/deflation of $\psi = 1.00$, the adjusted sample sizes are

	eta	n0	n1 (fix)	n1 (GSD)	N (fix)	N (GSD)
1	0	85	85	103	170	188
2	0.1	85	105	126	190	211
3	0.15	85	118	141	203	226
4	0.2	85	135	160	220	245
5	0.3	85	183	212	268	297
6	0.4	85	262	294	347	379
7	0.5	85	406	438	491	523
8	0.6	85	695	716	780	801

R Shiny app

https://power-implications.shinyapps.io/prod/



5 Regulatory and operational aspects

- **DMC**
  - If a trial is switched from fixed to adaptive design, a DMC needs to be established
  - The DMC charter of ongoing trials might need updating due to the new situation
- **Estimands**
  - The estimands framework is ideal for handling COVID-19 related intercurrent events
    - If you have not yet formulated your trial's objectives in the estimands framework, now is the perfect time to do so
  - Consider if you need to distinguish direct COVID-19 disease related intercurrent events from indirect intercurrent events caused by the lockdown measures
  - In case the estimand changes post pandemic, e.g. new exclusion of patient vulnerable to COVID-19, the trial results might be difficult to interpret
- **Type I error**
  - When changing a trial from fixed to adaptive design, the type I error should be maintained
  - Any unplanned change in the design of an ongoing trial is viewed critically. However, changes due to COVID-19 are clearly external to the trial which is less of a concern

Big “Thank you”...

- … to all members of the working group
  - Tim Friede, Christoph Gerlinger, Silke Jörgens, Frank Bretz, Nigel Stallard, Kelly van Lancker, Dong Xi, Sarah Zohar

- … to the Adaptive Designs Working group who brought up the issue
  - Werner Brannath and Lisa Hampson

- … to all of you for your attention.

Thank you!

Should we restart our paused trial? Deliberations and reflections from a case study

TMRP Webinar: 24 June 2020

Amanda Farrin, University of Leeds

UNIVERSITY OF LEEDS

Talk outline

Brief introduction to the case study: ISCOMAT

Trial progress pre-COVID

Why are we considering not restarting?

- Trial conduct considerations
- NHS & other considerations
- Trial design considerations
- Statistical power considerations

Statistical issues anticipated / scenario planning

NIHR RESTART framework

Cluster randomised trial of a complex intervention to improve medicines management for heart failure patients discharged home from hospital

Trial Design

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Definitive, pragmatic, multicentre cluster RCT + internal pilot.

Clusters randomised 1:1 to intervention or control.

P **HF diagnosis** within last 5 years. Recruited in cardiology wards

I **MaTI** : **Medicines at Transitions Intervention**



C Treatment as usual

O **<u>Primary</u>: All-cause mortality + HF rehospitalisation over 12m**

<u>Key Secondary</u>: on guideline indicated HF medications at 12m

Other secondary: time on HF meds; days alive & out of hospital;
Pt understanding of meds; pt satisfaction with meds/care;
EQ-5D; resource use at 3 & 12m; deaths; hospitalisations

From electronic records (NICOR, HES, ONS, GP) & pt questionnaire

S **2100 patients across 42 hospitals for 80% power**

(6% MCID, 20% control event rate; 0.01 ICC; 15% LTFU)

Trial Progress pre-COVID

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1641 patients recruited: 78% of full sample

- 44 sites randomised
- 43 opened to recruitment, 10 now closed
- ~ 100 patient / month

Overrunning on time

- Difficult to recruit in some clusters
- Difficult to maintain intervention fidelity in some clusters
- Funded extension required to complete the trial

Loss to follow-up

- Lower loss anticipated for primary outcome
- High loss for patient reported outcomes (secondary) 50-70%

Event rate not yet estimated – routine data

Rationale for no restart

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Proportion of target recruited to date

Unknown post-COVID landscape

- Clinical services delivering MaTI may look very different
  - Is intervention still relevant?
  - Can it still be delivered? In secondary & community care
- When will NHS heart failure services get back to research?
- Patients still willing?

Funding

Cluster trial design

- Need intervention & control sites recruiting post-COVID
- Refresher training for intervention sites?

Statistical considerations

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Power achieved:

- <80% primary but >90% key secondary
- Extend time to observe primary outcome event?
- Time to event analysis?
- Stop collecting any more secondary outcomes?

Changes to primary outcome due to COVID

- Differential effect between arms?
- Delayed hospital presentations?
- COVID impact on disease progression?

Impact on self-reported data during COVID-19

- Potential changes to questionnaire responses?
- Further reduce follow-up rates?

Sample size assumptions

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Composite primary event rate: at least 20% in control sites
MCID defined as 6%, intervention event rate 14%.

Power to detect MCID: 80%

Loss to follow-up: 15%

Clustering

- Estimated ICC of 0.01
- Cluster size of 50 HF patients in 42 clusters
- Variable cluster size, e.g. early clusters might recruit more
- Co-efficient of variation of cluster sizes < 0.23
- Cluster sizes 35 - 65 allowed; mean = 50

Statistical exploration

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Not planning interim or futility analysis on observed data:

- 12m primary outcome event = death or HF re-hospitalisation
- Acquired via routine data extract (HES/ONS) later in trial timeline

To inform decision on restart: reviewed sample size assumptions & explored alternatives

- Used data to date to estimate cluster size / variability
- Predicted withdrawal rate from primary outcome data extract
- Vary primary outcome definition – time to event vs proportion
- Extend follow-up time to observe more events
- Consider changed event rate due to COVID

Lower LTFU / Time to event?

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Primary outcome	Loss to follow-up	Power with 6% MCID TAU vs. MaTI 20% vs. 14%	Number of events / Hazard ratio	Difference detected with 80% power (TAU vs. MaTI) [relative % difference]
Proportion (original)	10%	**71%** (20% vs. 14%)		**6.6%** (20% vs.13.4%) [33%]
	15%	**69%** (20% vs. 14%)		**6.7%** (20% vs. 13.3%) [34%]
Survival rate	10%	**70%** (0.8 vs. 0.86)	257 / 0.670	**6.7%** (0.8 vs. 0.867) [34%]
	15%	**68%** (0.8 vs. 0.86)	243 / 0.679	**6.9%** (0.8 vs. 0.869) [35%]

Extend follow-up time?

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Optimistic scenario: intervention effect extends beyond >12m, for duration of extended F/U follow-up

- TAU event rate continues as observed
- MaTI event rate continues to be proportionally lower by x%.
- TMG considered this unlikely given plausible intervention effect

Power to detect 6% MCID > 70% (more TAU events)

Realistic scenario: intervention effect not maintained after 12m

- TAU event rate continues as observed
- MaTI event rate starts to increase
- Further work required to look at distribution of 'waning' effect
- Lack of existing data to estimate how close event rates are by 18m

Power reduces to 37% if intervention effect = 4% diff

Higher event rate?

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Higher rate plausible with COVID

- Mortality is part of primary outcome: event rate could increase due to COVID-19 eg beyond 20% expected in TAU
- Currently mortality by 12 months is 17%.
- Could assume increase in event rate proportional in both arms – but this is currently unknown.

Absolute or relative reduction?

- 6% **absolute** difference = 30% **relative** reduction (20% TAU rate)
- Power to detect 6% absolute reduction decrease, as event rate increases
- Power to detect 30% relative reduction increases, as event rate increases
- Which is more plausible?

Higher event rate?

Assume 6% absolute difference

Primary outcome	Loss to follow-up	TAU	MaTI	Power	Relative % difference
Proportion (original)	10% (current)	20%	14%	71%	30%
		25%	19%	62%	24%
		30%	24%	56%	20%
		40%	34%	50%	15%
Time to Event	10% (current)	0.20	0.14	70%	30%
		0.25	0.19	62%	24%
		0.30	0.24	56%	20%
		0.4	0.34	50%	15%

Assumptions for the power calculations: 2 sided test, 5% significance level, ICC estimate 0.01, unequal sizes in each treatment arm, coefficient of variation 0.55, 43 clusters, mean cluster size 38.4.

Higher event rate?

Assume 30% relative difference

Primary outcome	Loss to follow-up	TAU	MaTI	Power	Absolute % difference
Proportion (original)	10% (current)	20%	14%	71%	6%
		25%	17.5%	82%	7.5%
		30%	21%	90%	9%
		35%	24.5%	95%	10.5%
		40%	28%	98%	12%
Event rate	10% (current)	0.20	0.14	70%	6%
		0.25	0.175	81%	7.5%
		0.30	0.21	89%	9%
		0.35	0.245	95%	10.5%
		0.4	0.28	98%	12%

Assumptions for the power calculations: 2 sided test, 5% significance level, ICC estimate 0.01, unequal sizes in each treatment arm, coefficient of variation 0.55, 43 clusters, mean cluster size 38.4.

Restart Framework

Published: 21/05/2020 Read Time: 18 minutes Version: 1.0 21 May 2020 Print this document

A framework for restarting NIHR research activities which have been paused due to COVID-19

Purpose of this paper

The purpose of this paper is to set out a framework to guide the restarting of NIHR research activities which have been paused due to COVID-19.

The term 'NIHR research' refers to research either funded or supported by NIHR in healthcare, social care and public health settings.

The key aims of the framework are to guide:

1. the restart of paused NIHR research that was underway in the health and care system prior to the COVID-19 'surge',
2. the commencement of 'new' NIHR research, and
3. the prioritisation of resources in the NIHR Clinical Research Network (CRN) and NIHR infrastructure more broadly.

The framework sets out guiding principles, preconditions, study prioritisation, and local and national roles in implementing this 'Restart Framework'.

Background

Contents

NIHR RESTART framework

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TMG decision 'continue to pause'

'Only research that is still viable should restart/start - some studies that have been paused or have not yet started may no longer be viable, for scientific, clinical, financial or practical reasons. It would be unethical and a waste of money to restart/start studies that are no longer viable'

ISCOMAT unlikely to be viable

- Scientific integrity / clinical relevance / practical issues
- Clinical pathway / clinical capacity questions for sites
- Research capacity and site readiness

Finance required to extend

Currently seeking further site viability info to inform TSC, funder, etc

Final reflections

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Complex decision making process

Still robust trial results or not, if stopped?

Rapidly changing environment

Less rapidly evolving guidance from NIHR

Incomplete information to inform decisions / statistical considerations

Team science approach essential

Acknowledgements

ISCOMAT Trial team at CTRU: Ivana Holloway, Bonnie Cundill, Suzanne Hartley, Lauren Moreau, Emma McNaught, Alison Fergusson

ISCOMAT Chief Investigators: Chris Gale, Alison Blenkinsopp, Peter Gardner, Jon Silcock

ISCOMAT Programme Research Team: Beth Fylan, Hanif Ismail, David Alldred, Liz Breen

Disclaimer:

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The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health


QUESTIONS

Question	Answer
Really interesting talk, thank you! Are you only considering not re-starting due to efficacy? What about not re-starting due to futility - especially relevant if a dilution effect is expected?	Thanks for your question. I think it is a mix of both. For the GSD, we only put in early stopping for efficacy (not futility). However, you could also put in both options (which will come with a loss in power or a larger sample size to make up for the power). If you expect a dilution effect that is purely down to missed treatments or other logistical issues, there is another option you could explore: wait until the logistical issues are resolved and then restart the trial. This might still be faster than adjusting the sample size. I discuss this option in the new version we hope to submit on Friday. The reason we did not consider pure stopping for futility is that COVID-19 is truly an external unplanned event and usually it should not affect the mode of action of the compound under investigation. Hence, there is not really a need to stop for futility (based on a smaller treatment effect that is due to the treatment itself, i.e. independent of COVID-19).
Yes that's true - so I'll set dilution aside. Still, I thought your overall idea was to do an unplanned interim analysis to see if it is worthwhile restarting the trial, and futility would be as good a reason to not restart as efficacy?	Even though we did not formally put a futility stop in, it is not a problem in terms of type I error rate to analyse the data at interim and then decide not to continue the trial. This will only affect the overall power. However, if you have already seen the data and decided it is not worth continuing, power is not really a concern anymore.
Scenario: A trial is 75% through recruitment, but it was always challenging, and there are concerns about motivation to restart. We can calculate the power using the original estimates and number recruited so far, and decide on that basis. However, given that the estimate of the control group event rate used originally was not necessarily based on great data, should we use the data collected so far to estimate this nuisance parameter and update the power calculation? What would the issues be with this approach?	This sounds like an unblinded sample size reassessment, if you look at the control group separately. These methods have been published and it might be useful to have a deeper look into this. However, you will have to adjust the analysis to account for this interim look. If the original trial was planned on uncertain parameters, it would have been a good option to think about sample size reassessment (even without COVID-19). I guess one thing to keep in mind is that while the original assumption might be wrong, the estimated response rate is still an estimator and might not necessarily be better.
Is there anything to learn from all this that we will take forward into the post-COVID world, e.g. about flexibility, contingency planning, trial 'burden', trial robustness or anything else?	*Answered by the presenters verbally at the end of the webinar*