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

**Methodological issues in global health trials**

***Duolao Wang (Liverpool School of Tropical Medicine)***

***Elizabeth Allen (University of Cape Town)***

***Sile Molloy (St Georges University London)***

8 November 2021

On behalf of the Global Health Network

The slides are also available below.

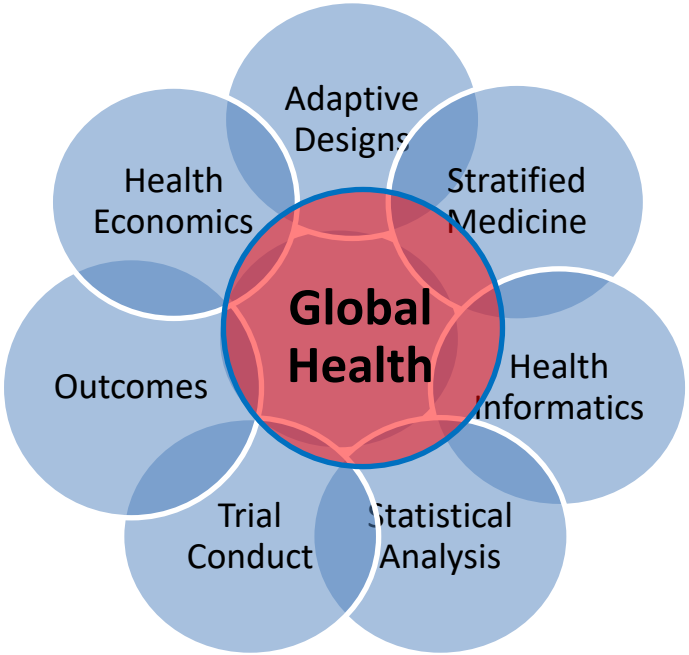
For any queries, please contact uktmn@nottingham.ac.uk

**https://www.youtube.com/watch?v=wcEHLd7FX10**

# The Trials Methodology Research Partnership (TMRP)

- The TMRP began in June 2019 following funding awarded by the MRC-NIHR Methodology Research Programme. The Partnership is led by Professor Paula Williamson, University of Liverpool.
- The mission is to improve the design, conduct, & analysis of trials everywhere
- The TMRP brings together a number of networks, institutions and partners working in trials and trials methodology research.
- The five TMRP partner networks:
  - The Global Health Network (TGHN)
  - Health Research Board - Trials Methodology Research Network (HRB-TMRN)
  - Health Data Research UK
  - UKCRC Registered CTU Network
  - UK Trial Managers' Network (UK TMN)

# TMRP Working Groups

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# Global Health Working Group

**https://www.methodologyhubs.mrc.ac.uk/about/working-groups/**

**Objectives are to**:

1) Raise awareness of the field and scope of clinical trial methodology research to those in LMICs

2) Interact with the other Working Groups of the TMRP (Stratified Medicine, Health Informatics, Adaptive Designs, Outcomes, Trial Conduct, Health Economics, and Statistical Analysis)

3) Further increase the capacity for trial methodology research in LMICs through freely accessible information

4) Respond to queries from those in LMICs wanting guidance on methods, potential collaborators and training opportunities/events

5) **Manage small pump-priming grants for LMIC clinical trials methodology research projects**

- **Join Working Groups & interact with a large, diverse membership**
- **Visit TMRP websites for guidance, publications, webinars, networking**
- **Hear about grant opportunities**

| Country | Title |
|---|---|
| Uganda | The practice of **pilot studies** in informing the conduct of HIV clinical trials in sub Saharan Africa: a review of study protocols |
| Kenya | Pilot implementation of **Short Message Service for randomisation** in a multisite pragmatic factorial clinical trial in Kenya (PRISMS Study) |
| Uganda | **Photovoice to explore community members perspectives** regarding health and healthcare challenges in Mukono District, Uganda |
| Tanzania | Assessment of the **challenges encountered in implementing vaccine clinical trial** methodologies in low income countries |
| UK/India | **Optimising Informed CONsent** in clinical trials in low- and middle-income settings: feasibility of an adapted QuinteT Recruitment Intervention (QRI) in India (OrION-I) |
| Thailand | Exploring **barriers to data reuse** |
| South Africa | **Cultural competence in trial design and conduct** |


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The Global Health Network enables easier, faster, and better research in the world's most challenging settings.
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Transferring knowledge and exchanging methods, processes and research findings between diseases, regions and organisations.
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About
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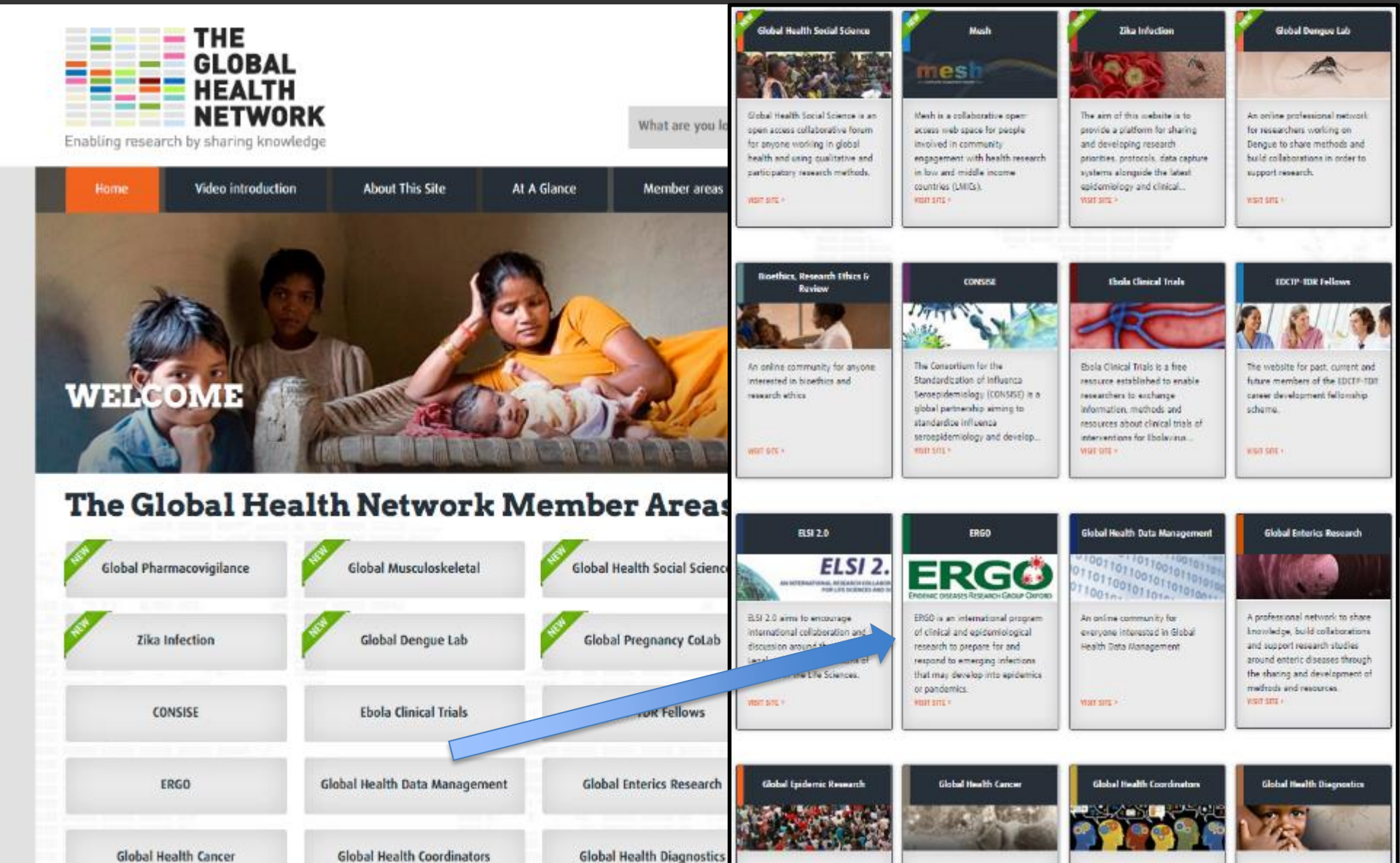
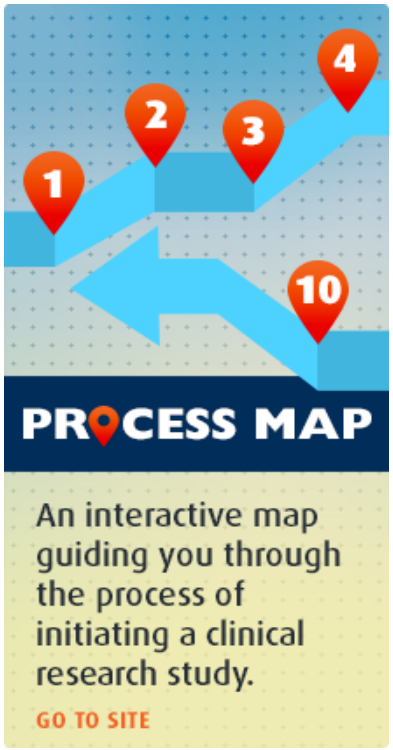
# An online science park for global health researchers; working space for groups, mechanism for knowledge exchange, training & access to tools, templates & guidance

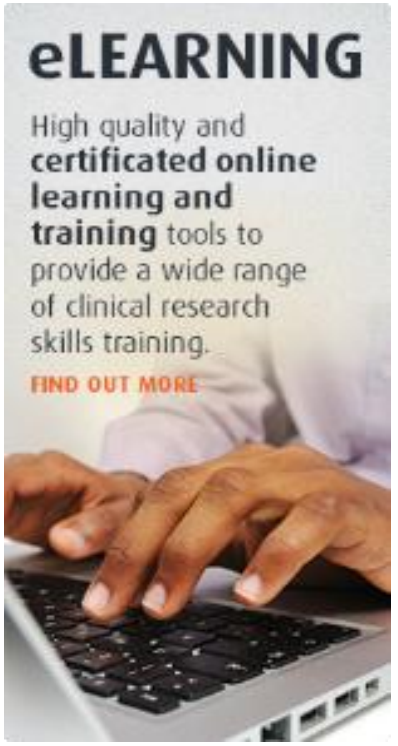


# Providing applications to enable & speed-up research

THE GLOBAL HEALTH NETWORK
Enabling research by sharing knowledge





# COVID-19

Research Implementation and Knowledge Hub

*Supporting Equitable Access to Conducting Research Across the Globe*



## Home

The ability to undertake research should be equitable across the globe and we need to engage in all types of studies across all settings and care contexts.

The **aim of this hub** is to ensure that research teams can find the support, tools, resources and guidance that they need to aid their studies during this rapidly evolving situation. Using shared and open protocols and tools can raise research standards and enable easier and better data sharing.

### WORKING GROUPS

Implementing research studies during this pandemic can be made faster and easier by working collaboratively

### REGIONAL RESPONSE

Working collaboratively and sharing information resources across regions

### RESEARCH IMPLEMENTATION

Find guidance, open access protocols, tools and resources on 7 different thematic areas

### OPEN WORKSHOPS

TGHN host regular online interactive workshops to facilitate learning and discussion around important research questions

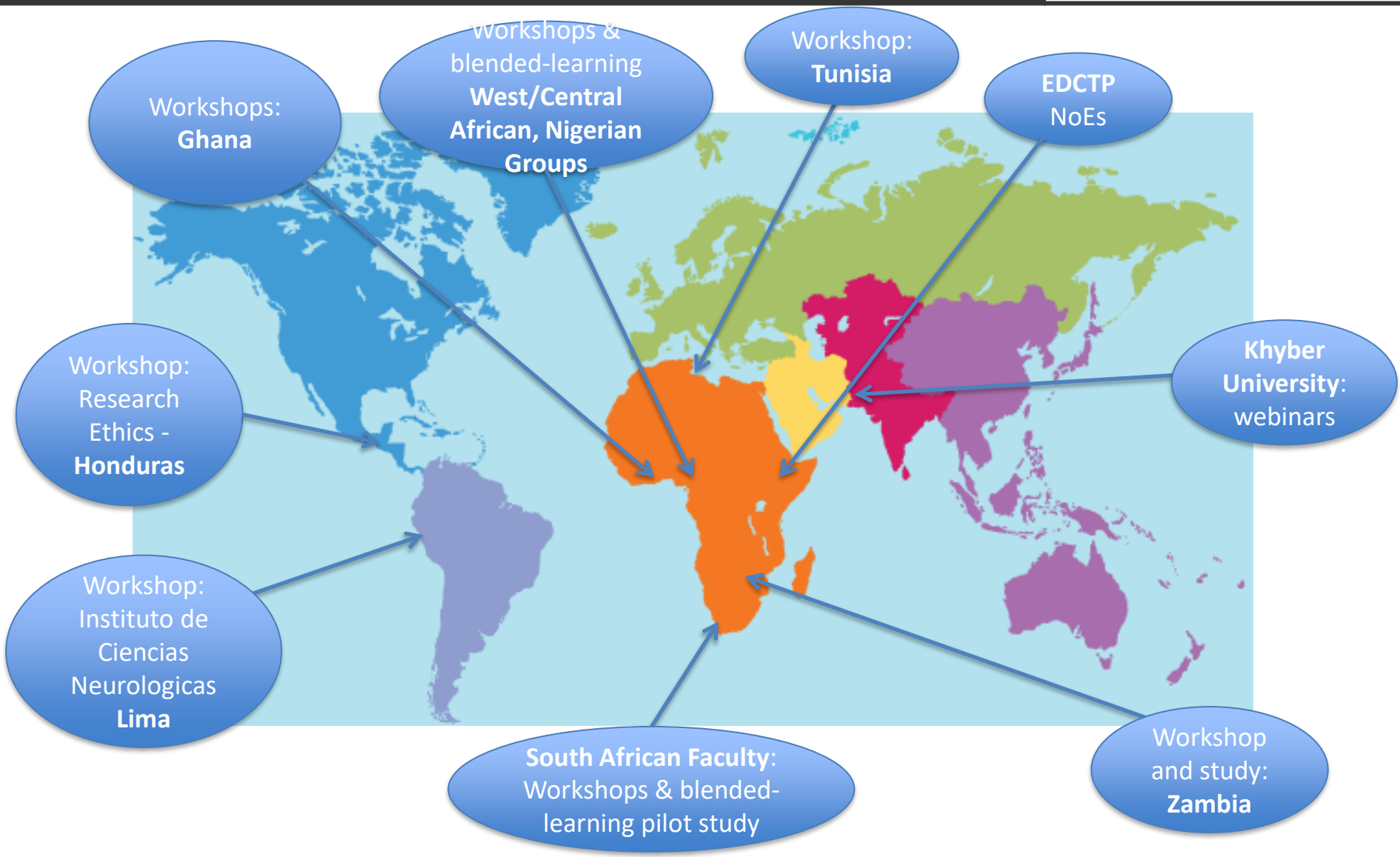
### STUDY PROFILES

Research teams conducting

### RESEARCH RESOURCES

# Regional Faculties & Workshops

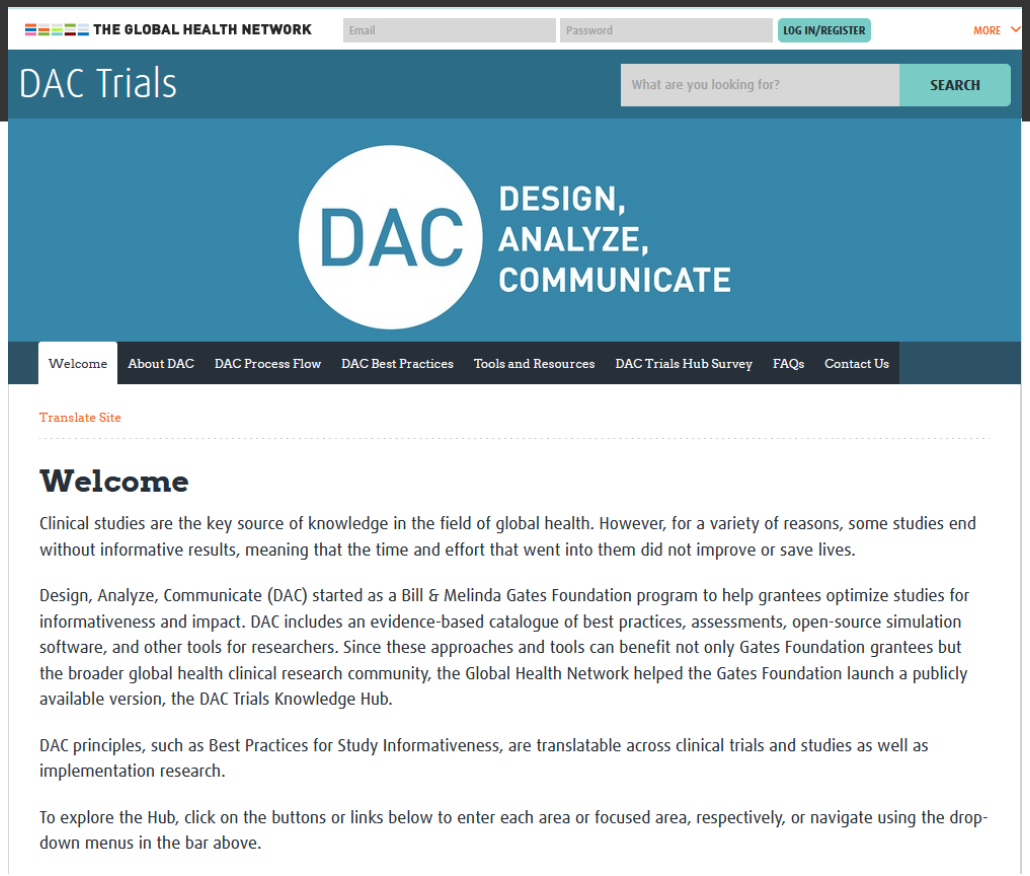
THE GLOBAL HEALTH NETWORK
Enabling research by sharing knowledge



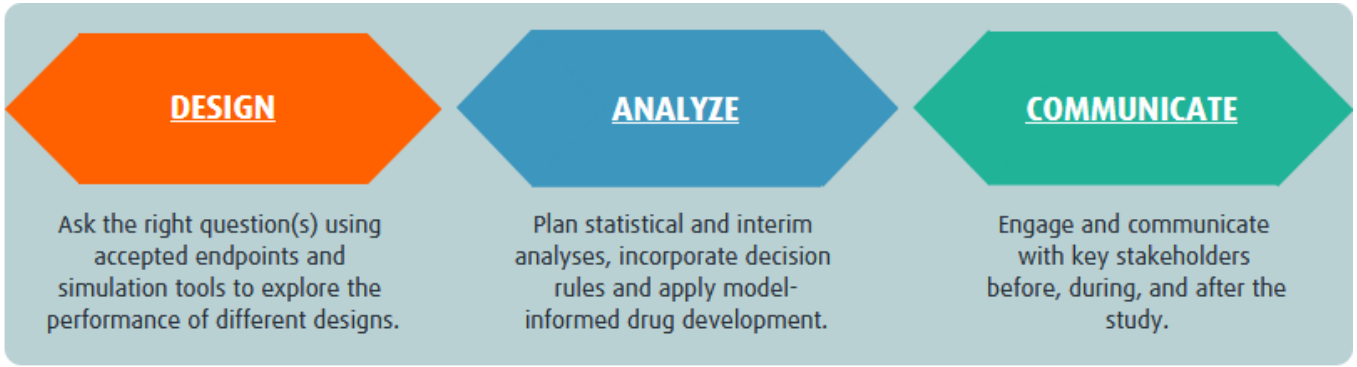
# BMGF DAC Trials hub

THE GLOBAL HEALTH NETWORK

Enabling research by sharing knowledge




- A program to help grantees optimise studies for informativeness & impact
- Evidence-based catalogue of best practices, assessments, open-source simulation software, & other tools
- Now publicly available, translatable across trials, implementation research



# DAC best practices

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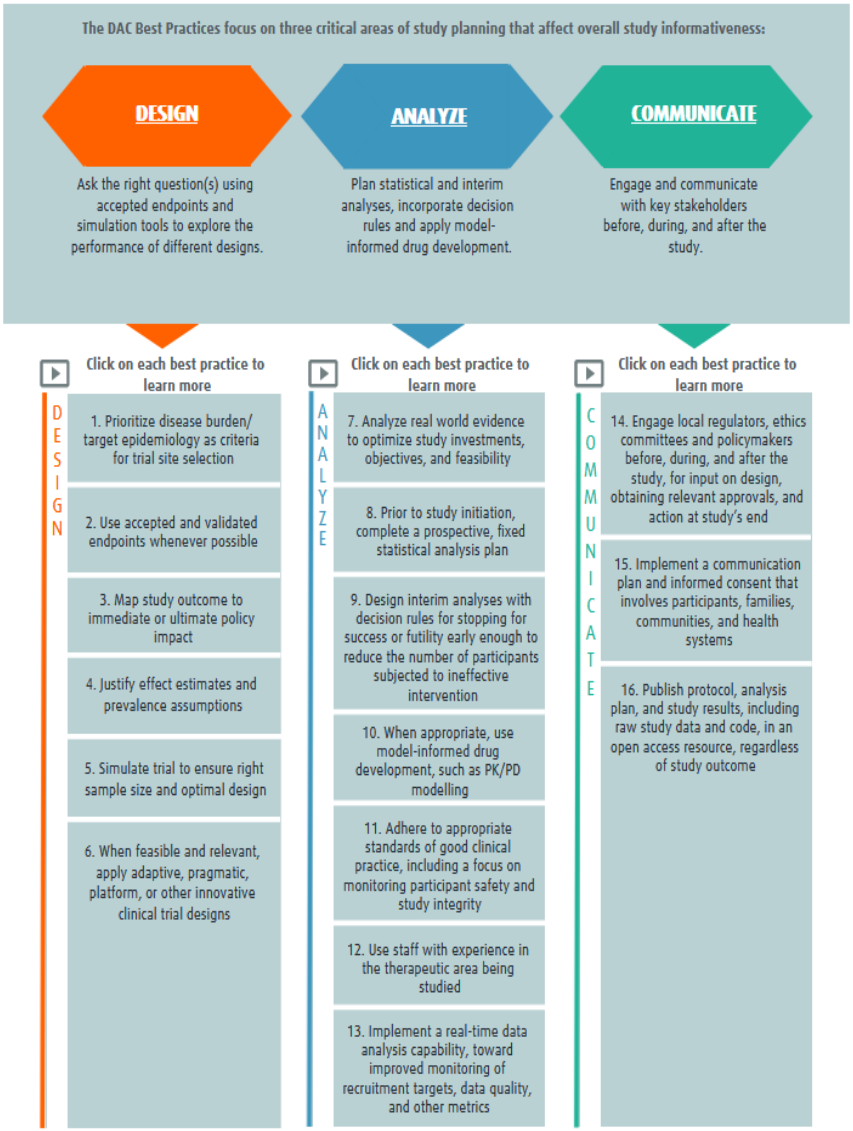


## Best Practices Video Resources

**Best Practices for Informativeness in Clinical Research**

This series of informative videos presented by global experts provide detail on each of the DAC Best Practices. Find out more about what the Best Practices are, why are they important, and how implementing them can help you deliver an informative study. The following resources are split into the three DAC aspects - Design, Analyze and Communicate. Browse the videos by each theme below.

(D)AC - DESIGN ASPECTS | D(A)C - ANALYZE ASPECTS | DA(C) - COMMUNICATE ASPECTS

**(D)AC - Design aspects**

**1. Prioritize disease burden and epidemiology as criteria for study site selection** ***(click thumbnail to play)***


**(D)AC - Design aspects**

**2. Use accepted and validated endpoints whenever possible** ***(click thumbnail to play)***

# DAC tools & resources

THE GLOBAL HEALTH NETWORK
Enabling research by sharing knowledge


**Please visit the site & take part in the survey**

https://dac-trials.tghn.org/

# DAC tools cont.

THE GLOBAL HEALTH NETWORK
Enabling research by sharing knowledge

- DAC Assessment Tool (DAT): questions for trial teams to consider important elements
- Mediana simulation software: power & sample size calculations for designing late-stage trials, incl. adaptive designs in Phase III & seamless Phase II/III trials
  - Adaptive designs with data-driven sample size or event count re-estimation, adaptive designs with data-driven treatment or population selection, optimal selection of futility stopping rule, event prediction in event-driven trials, adaptive designs with response-adaptive randomisation, traditional designs with multiple objectives
- Global Center for Gender Equality, Stanford University: translating gender data, research, analysis & theory into evidence-based, practical applications: best practices for sex-gender considerations in clinical trials
  - Collecting and reporting data, investigation of sex-gender factors, eligibility criteria supporting representative sampling, sensitivity to gender aspects of recruitment, retention & adherence, differentiation analyses of sex-gender that are hypotheses-driven
- Target Policy Profile Overview (TPoP) tool: facilitating dialogue around evidence needed to effect a change in policy
- Resources data base; searchable, interactive access to relevant tools & resources on the DAC Knowledge Hub & TGHN
- Protocol library; large collection of LMIC protocols with various design decisions, approaches to statistics, recruitment, communication & GCP that might provide ideas for future teams

# Multiplicity adjustment:

x

# A requirement for all multi-arm trials?

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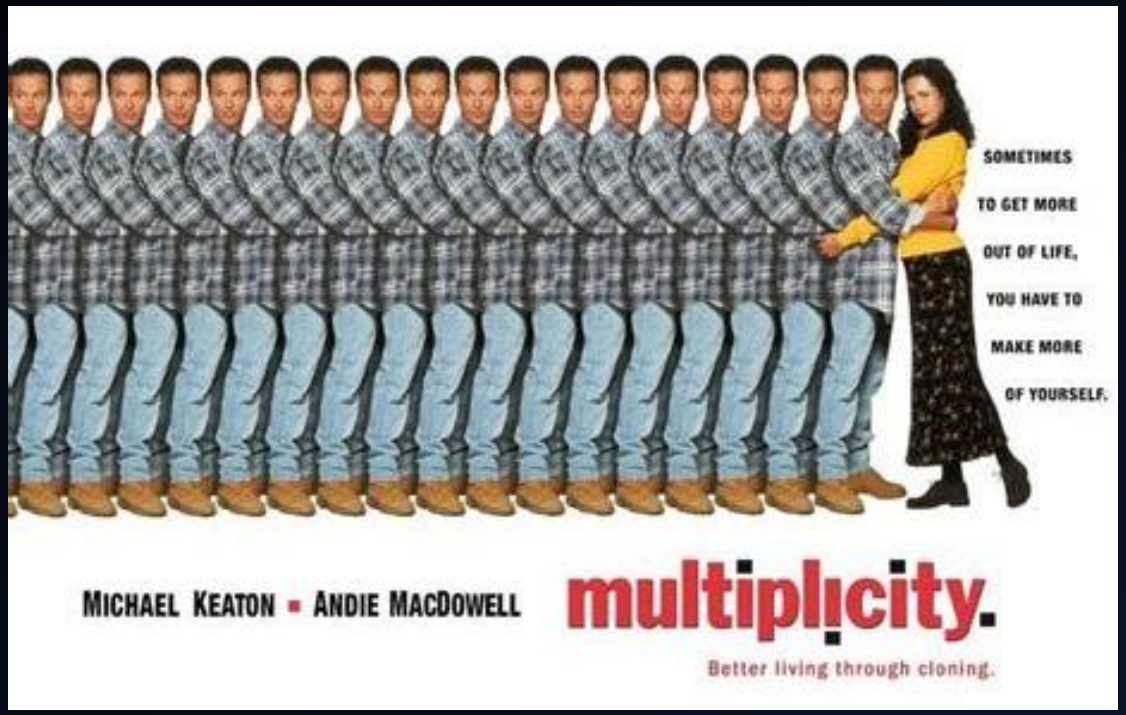
8TH NOVEMBER 2021


SOMETIMES
TO GET MORE
OUT OF LIFE,
YOU HAVE TO
MAKE MORE
OF YOURSELF.
MICHAEL KEATON • ANDIE MACDOWELL
multiplicity.
Better living through cloning.

# Introduction

- What is multiplicity?
- Adjusting for multiplicity
- Multiplicity adjustment in multi-arms trials
  - A personal perspective….
  - Background to multi-arm trials and adjustment
  - Lack of/inconsistent guidance
  - Issues with multiplicity adjustment
- Conclusion / recommendation

# What is multiplicity?

- Multiple significance tests carried out increasing the family-wise type-I error rate (FWER)

  → the probability of making at least one “false positive” conclusion among all the multiple hypotheses tested

- Multiplicity can arise for various reasons
  - Multiple outcomes
  - Repeated measures
  - Interim analyses
  - Multiple sub-groups
  - Factorial designs
  - Multi-arm clinical trials

# Adjusting for multiplicity

- Multiple testing procedures
  - Statistical methods of adjusting the significance level used for testing each hypothesis so that the chance of making a type-I error is controlled
- Various methods of control have been developed
  - Hierarchical procedures (e.g. fixed-sequence, gate-keeping)
  - Bonferroni method
  - Dunnett's test
- If not handled correctly, unsubstantiated claims for effectiveness of a drug may be made
- However, if applied unnecessarily, potentially effective treatments may be discarded
- ??Multi-arm parallel trial designs

# From a reviewer perspective…

*"The manuscript reports a multitude of comparisons, thus generating the need to adjust for m… addr… docu…*

*"We have not done any adjustment for multiplicity of inferences. The primary objective of the study was to determine (separately) the effects of the… [treatments]… compared with the recommended gold standard therapy …. It was believed that the effects of …[the new therapies]… on the primary outcome are independent. These were clinically driven a priori hypotheses. Therefore, we believe that no adjustment for the two primary comparisons was neces… natur…*

…ndard of care

- N… se… co…

*" Control for multiplicity of inferences:*
*The issue is broad, has been central in the design and reporting of randomized studies, and is increasingly becoming a concern in reporting of observational studies. The heightened relevance of controlling for multiplicity of inferences parallels the recent public attention to the problem with the reproducibility of scientific results. Control for multiplicity is routinely applied in clinical trials with multiple endpoints, and often includes both primary and secondary, irrespectively of whether they were pre-specified…"*

*For the primary aim, please report the 97.5% CIs in the results and abstract. These are the most relevant to the reader and do not constitute sensitivity analysis.*

# Multiplicity adjustments in multi-arm trials sharing a control group: clear guidance is needed

Authors:
Síle F Molloy, Lecturer in Epidemiology*¥[1]
Ian R White, Professor of statistical methods for medicine*[2]
Andrew J Nunn, Senior Scientist & Professor of Epidemiology[2]
Richard Hayes, Professor of Epidemiology and International Health[3]
Duolao Wang, Chair in Biostatistics [4]
Thomas S Harrison, Professor of Infectious Diseases and Medicine,[1]

*Joint contribution ¥Corresponding author

# Background - Multi-arm trials are good!

- Multi-arm trial designs are valuable in clinical research
  - A number of new treatments tested within a single trial
  - Increases efficiency (shared information)
  - Reduces costs and administrative burden

- 3-arm trial → Sample size reduced by 25% compared to what would be required for 2 independent trials (efficient sharing of the control group)

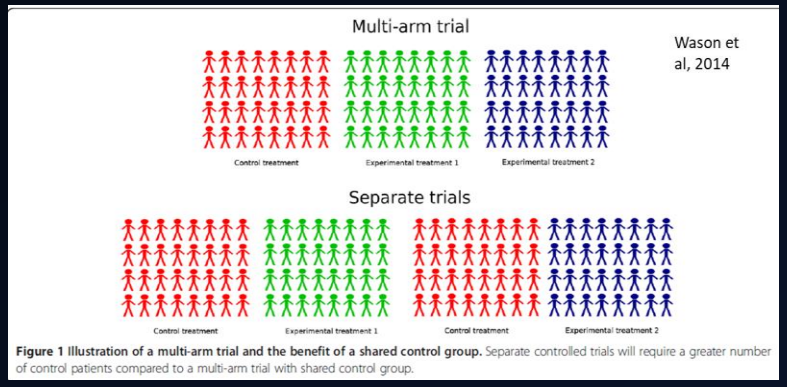



**Figure 1 Illustration of a multi-arm trial and the benefit of a shared control group.** Separate controlled trials will require a greater number of control patients compared to a multi-arm trial with shared control group.

# Background – Adjustment in multi-arm trials

17.8% published RCTs in 2009 were multi-arm design[1]

Some 20% of superiority trials registered in 2010-2012 had more than two groups[2]

**<u>2014 review</u>**:
49% of published multi-arm report mul a

More common in trials evaluati multiple regim sam

Little difference in adjustment between exploratory and confirmatory trials[3]


1. Baron et al. (2013), BMC medicine;11(1):84
2. Parmar et al. (2014), Lancet;384(9940):283-4
3. Wason et al (2014). Trials. 2014;15(1):364

# When should multi-arm trials adjust for multiplicity? - Lack of / Inconsistent guidance

- General consensus – For any multi-arm exploratory trial stringent multiple-testing adjustment is not required
- Many authors agree with current guidance from the FDA and EMA that for confirmatory trials where arms represent several doses or regimens of the same treatment, adjustments for multiplicity should be applied [4,5,6]
- However, the literature is unclear on the necessity of adjustment in confirmatory parallel multi-arm trials where the different arms represent separate treatments and are compared against a shared control

# When should multi-arm trials adjust for multiplicity? - Lack of / Inconsistent guidance

- A number of authors argue that adjustment is not always necessary, particularly where the results are not combined into one final conclusion and decision[3,7-9]
- By contrast, guidance from the New England Journal of Medicine (NEJM) requires adjustment in this scenario, even for exploratory analysis[10]
- No consensus, across stakeholders such as regulators and scientific journals, on the necessity to control for a potentially inflated type 1 error rate when comparing distinct treatments to a shared control[1]

# Issues with multiplicity adjustment

- The key issue in determining whether to control for multiplicity is whether multiple tests are conceptually related: How separate are the scientific questions or the claims to be made?
- Multiple doses of the same drug - A claim of efficacy of the drug could be made if any one dose shows benefit, so multiplicity should be controlled
- Drugs with different mechanisms of action - argue that control for multiplicity is not required, just as if they were evaluated in separate trials
- The definition of “family” over which FWER should be controlled is crucial
- The difficulty with making treatment the ‘family’ is whether closely related treatments should be included in the same family: e.g. drugs of the same class, or similar multi-drug regimens

# Further considerations

- False discovery rate (FDR) - expected proportion of rejected null hypotheses that are actually true
  - Control FDR rather than the FWER → limits the expected proportion of ineffective drugs among the drugs that are successful (using Benjamini–Hochberg procedures)
  - Wason et al. 2021 recommend that sponsors and trialists consider use of the FDR for multi-arm trials testing distinct treatment arms with others suggesting the FDR as an appropriate control measure in the context of trials with a large number of treatments

- Common control group
  - Adjustment required as treatment comparisons are related in this way? Howard et al[4] demonstrated this concept is false and the FWER is not increased in this case

# Conclusion / recommendation

- Clearer guidance for trialists on the appropriate settings for adjustment of multiplicity is required
- We propose that adjustment should not be a requirement in multi-arm, parallel design trials testing distinct treatments and sharing a control group
- Further clarity is needed to define what are distinct treatments - careful consideration required

# THANK YOU!

- Ian R White, Professor of statistical methods for medicine, UCL
- Andrew J Nunn, Senior Scientist & Professor of Epidemiology, UCL
- Richard Hayes, Professor of Epidemiology and International Health, LSHTM
- Duolao Wang, Chair in Biostatistics, LSTM
- Thomas S Harrison, Professor of Infectious Diseases and Medicine, SGUL

## QUESTIONS / DISCUSSION

# References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12. European Medicines Agency. Guideline on Multiplicity Issues in Clinical Trials 2017 11 August 2020. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf.
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# Design and analysis of global health trials using win ratio approach

Duolao Wang

Professor of Biostatistics

Liverpool School of Tropical Medicine

TMRP Methodology webinar

**Methodological issues in the design and analysis of global health trials**

**8 November 2021**

# Topics

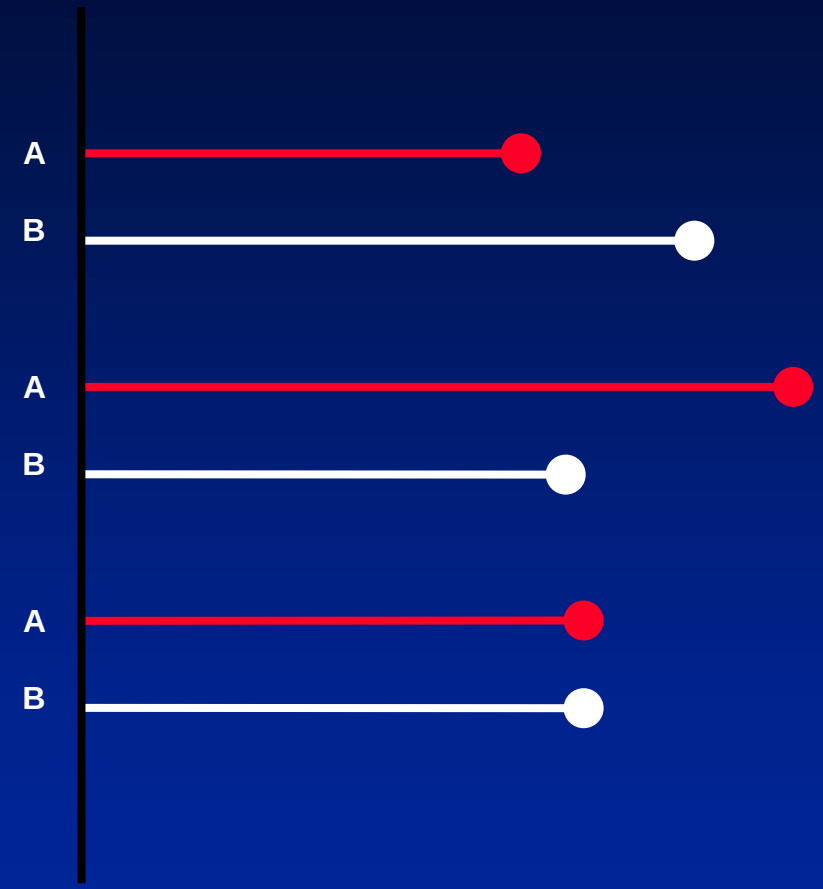
1. Win ratio statistic
2. Applications of win ratio method
3. Recent methodological developments on win ratio
4. Statistical software package for win ratio analysis
5. Summary

# 1. Win ratio statistic

- The original use of the win ratio was for a hierarchy of composite time to event outcomes (Pocock et al 2012 EHJ).

- The win ratio method is essentially based on the counts so-called “winner” and “losers” in each treatment group for an outcome among all possible pairwise comparisons.

# Determine the winner and loser




A wins

A loses

Tied or no winner

The larger the value, the worse the diagnosis

# How to calculate win ratio statistic

- Win ratio statistic:
  - Step 1: Patients in treatment A ($N_A$) and B ($N_B$) are formed into all possible **pairs** ($N_A$ x $N_B$);
  - Step 2: For **each pair** the treatment A patient is labelled a “winner” or a “loser” or a “tied” according to their outcomes;
  - Step 3: Calculate the total number of winners ($N_W$), losers ($N_L$), and tied ($N_T$). $N_W + N_L + N_T = N_A \times N_B$.
  - Step 4: $Rw = N_W/N_L$ is the “win ratio”, the statistic for assessing the treatment effect for an outcome in a clinical trial

# A working example

A randomised clinical trial was conducted to assess the effect of the new therapy in terms of HYHA (heart function index: the lower the value, the better the heart function) compared to a standard therapy. The result is shown in the following table:

| Treatment A | | Treatment B | |
|---|---|---|---|
| ID | NYHA | ID | NYHA |
| 1 | 1 | 6 | 1 |
| 2 | 1 | 7 | 2 |
| 3 | 2 | 8 | 3 |
| 4 | 3 | 9 | 3 |
| 5 | 4 | 10 | 4 |

# Calculation of win ratio statistic

- Win ratio statistic:
  - Step 1: Patients in treatment A ($N_A$) and B ($N_B$) are formed into all possible **pairs** ($N_A$ x $N_B$);

    $N_A$ =5, $N_B$ =5,  $N$=35
  - Step 2 : For **each pair** the treatment A patient is labelled a “winner” or a “loser” or a “tied” according to their outcomes;

# Calculation of win ratio statistic

- Step 3: Counting the numbers of winners, losers and ties

| ID | | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|
| | NYHA | 1 | 2 | 3 | 3 | 4 |
| 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| 2 | 1 | 0 | 1 | 1 | 1 | 1 |
| 3 | 2 | -1 | 0 | 1 | 1 | 1 |
| 4 | 3 | -1 | -1 | 0 | 0 | 1 |
| 5 | 4 | -1 | -1 | -1 | -1 | 0 |

**1=Winner, -1=Loser, 0=Tied ➔** $N_W$**=12,** $N_L$ **=7,** $N_T$ **=6**

- Step 4: “win ratio” = *R*w = $N_W/N_L$ =12/7=1.71

# Interpretation of a win ratio

- The concept of a win ratio is relatively easy to understand and interpret, and provides an informative estimate of treatment difference. For example, the estimated win ratio >1 between treatment A and B means the treatment effect is

  in favour of treatment A to B. The estimated win ratio of 2.00 between treatment A and B suggests that among all possible comparisons between A and B, treatment A wins on average 2 out of 3 times that of B.

# Inferential statistics for win ratio

$H_0$: win ratio=1. There is no difference in number of "winners" between treatment A and B.

$H_a$: win ratio≠1. There is a difference in number of "winners" between treatment A and B.

- A significant test statistic for the above hypothesis of win ratio cannot directly be established due to the fact that the $N_A$ x $N_B$ pairs are not independent comparisons.
- Asymptotic theories have been established to calculate the P-value for the above hypothetic test and 95% CI. The computer intensive method such as the bootstrap can also be used to calculate 95%CI.

# 2. Applications of win ratio method

- **Examples of endpoints in clinical trials which are suitable for win ratio method**

- Composite endpoint
  - Time to the first occurrence of CV death, non-fatal MI, non-fatal stroke
  - Time to the first occurrence of death or disease progression

- Ordinal and non-Normal outcomes
  - Severity of adverse event (Mild, Moderate, Severe)
  - New York Heart Association (NYHA) (I,II,III, and IV)
  - Hospital stay (in days)

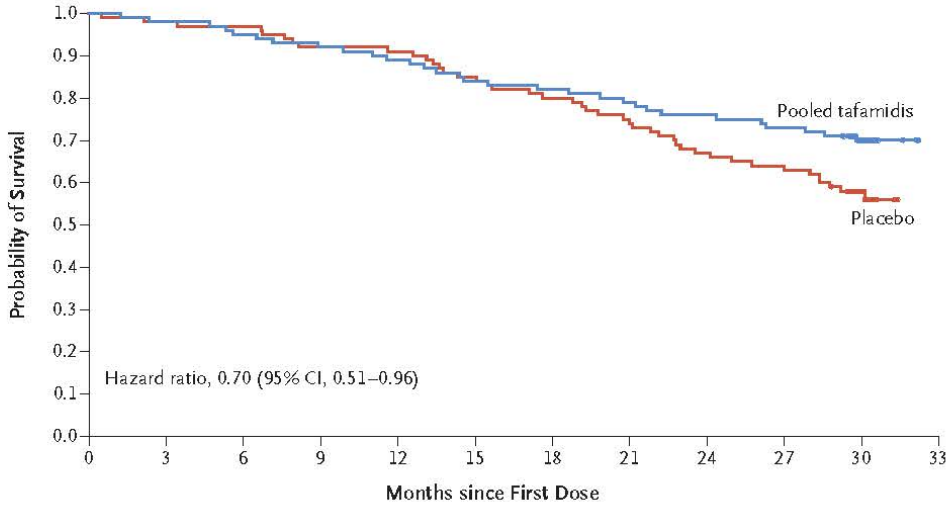
# Composite endpoint and its limitations

- Major RCT's in CV disease use composite endpoints as the primary outcome to assess the treatments efficacy
  - Analysis focuses on time to the first event
    - Usually Cox model, KM plots, log-rank tests used for reporting treatment effects
- Implicitly treat all contributory endpoints as equal
- Typically only takes account of the first occurring endpoint
  - Non fatal events occurring earlier in follow-up tend to get a higher priority than later more serious events and deaths
  - Survival curves may cross over

**A** Primary Analysis, with Finkelstein–Schoenfeld Method

| | No. of Patients | P Value from Finkelstein–Schoenfeld Method | Win Ratio (95% CI) | Patients Alive at Mo 30 | Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 |
|---|---|---|---|---|---|
| | | | | *no. (%)* | *per patient per yr* |
| Pooled Tafamidis | 264 | <0.001 | 1.70 (1.26–2.29) | 186 (70.5) | 0.30 |
| Placebo | 177 | | | 101 (57.1) | 0.46 |

**B** Analysis of All-Cause Mortality




No. at Risk (cumulative no. of events)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pooled tafamidis | 264 (0) | 259 (5) | 252 (12) | 244 (20) | 235 (29) | 222 (42) | 216 (48) | 209 (55) | 200 (64) | 193 (71) | 99 (78) | 0 (78) |
| Placebo | 177 (0) | 173 (4) | 171 (6) | 163 (14) | 161 (16) | 150 (27) | 141 (36) | 131 (46) | 118 (59) | 113 (64) | 51 (75) | 0 (76) |

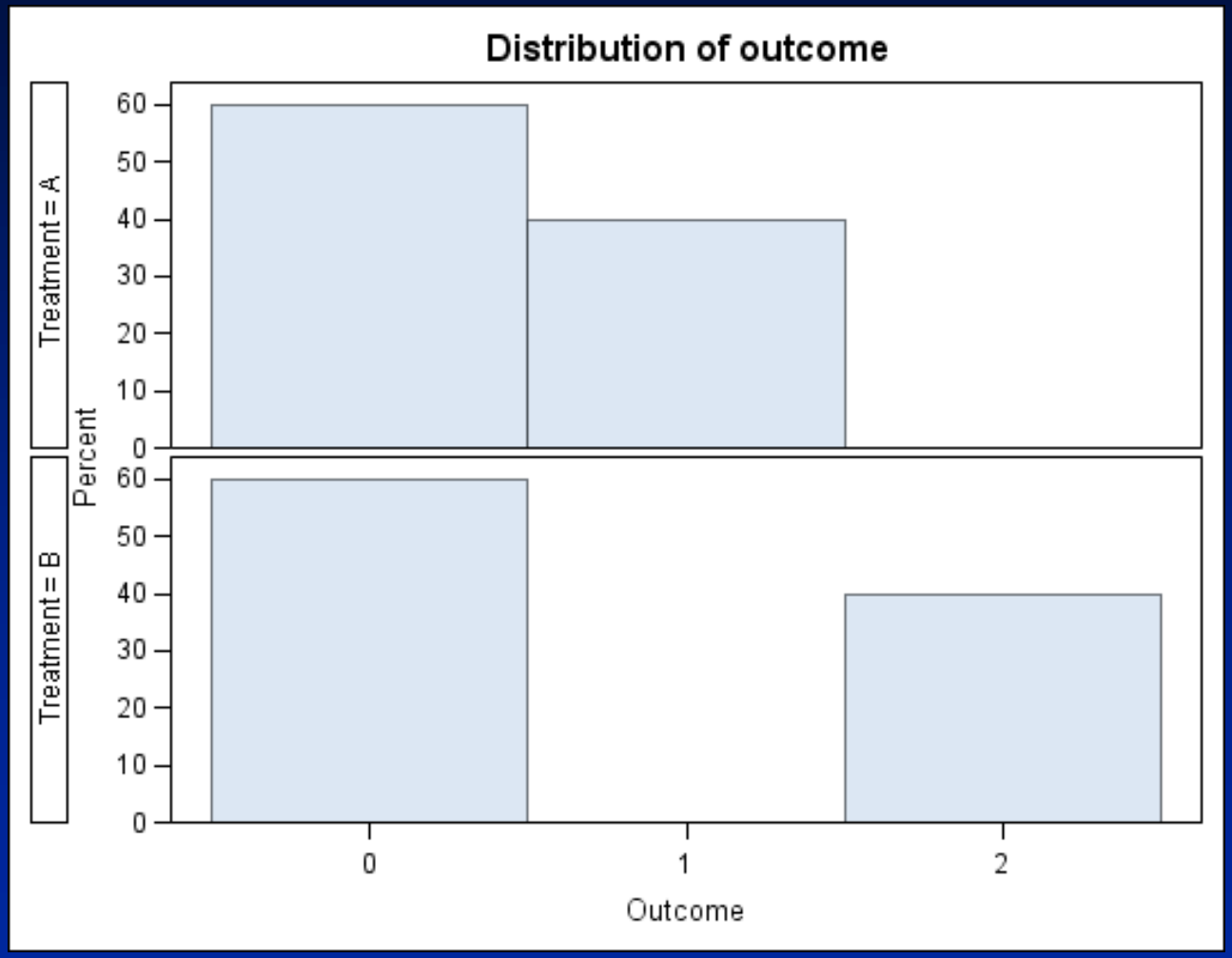
**C** Frequency of Cardiovascular-Related Hospitalizations

| | No. of Patients | No. of Patients with Cardiovascular- Related Hospitalizations | Cardiovascular- Related Hospitalizations | Pooled Tafamidis vs. Placebo Treatment Difference |
|---|---|---|---|---|
| | | *total no. (%)* | *no. per yr* | *relative risk ratio (95% CI)* |
| Pooled Tafamidis | 264 | 138 (52.3) | 0.48 | 0.68 (0.56–0.81) |
| Placebo | 177 | 107 (60.5) | 0.70 | |

**Figure 2. Primary Analysis and Components.**

Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.

# Non-normal outcome and its analysis



# Non-parametric methods and their problems

- The Mann-Whitney (MW) test *P*=0.0258,
- The median in both treatment groups is 0.
- Hodges–Lehmann (HL) “shift” statistic 0 and 95% CI = (0.0, 0.0).
- So both MW and HL methods generate misleading results of treatment effect for the above hypothetical trial
- Win ratio gives a win ratio estimate being 1.67, 95%CI=1.07,2.69.
- Wang D, Pocock S. A win ratio approach to comparing continuous non-normal outcomes in clinical trials. Pharm Stat. 2016; 15:238-45.

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019 Nov 21

We analyzed the total symptom score on the Kansas City Cardiomyopathy Questionnaire as a composite, rank-based outcome, incorporating patient vital status at 8 months along with a change in score from baseline to 8 months in surviving patients, using the rank analysis of covariance method, with a corresponding win ratio used to estimate the magnitude of treatment effect.[17] We assessed the consistency of

# Applications of win ratio in medical journals

- NEJM.
- Lancet
- Lancet Diabetes Endocrinol
- JAMA
- EHJ.
- JCC
- Journal of Clinical Epidemiology
- Contemp Clin Trials
- Clinical Trials
- Am Heart J

# 3. Recent methodological developments on win ratio

## Asymptotic theory on win method

1: Luo X, Tian H, Mohanty S, Tsai WY. An alternative approach to confidence interval estimation for the win ratio statistic. Biometrics. 2015 Mar;71(1):139-145.

2: Bebu I, Lachin JM. Large sample inference for a win ratio analysis of a composite outcome based on prioritized components. Biostatistics. 2016 Jan;17(1):178-87.

3: Dong G, Li D, Ballerstedt S, Vandemeulebroecke M. A generalized analytic solution to the win ratio to analyze a composite endpoint considering the clinical importance order among components. Pharm Stat. 2016 Sep;15(5):430-7.

4: Luo X, Qiu J, Bai S, Tian H. Weighted win loss approach for analyzing prioritized outcomes. Stat Med. 2017 Jul 10;36(15):2452-2465.

## Adjusted win ratio by covariates and censoring

1: Gasparyan SB, Folkvaljon F, Bengtsson O, Buenconsejo J, Koch GG. Adjusted win ratio with stratification: Calculation methods and interpretation. Stat Methods Med Res. 2021 Feb;30(2):580-611.

2: Dong G, Huang B, Wang D, Verbeeck J, Wang J, Hoaglin DC. Adjusting win statistics for dependent censoring. Pharm Stat. 2021 May;20(3):440-450.

3: Brunner E, Vandemeulebroecke M, Mütze T. Win odds: An adaptation of the win ratio to include ties. Stat Med. 2021 Jun 30;40(14):3367-3384.

## Trial Design

1: Peng L. The use of the win odds in the design of non-inferiority clinical trials. J Biopharm Stat. 2020 Sep 2;30(5):941-946.

2. Mao L, Kim K, Miao X. Sample size formula for general win ratio analysis. Biometrics. 2021 May 28

# 4. Win ratio packages

- Winratio_Bootstrap. SAS-based package for calculating win ratio for composite endpoints and non-normal data analysis by Duolao Wang
- WWR: An R package for analyzing prioritized outcomes by Junshan Qiu, Xiaodong Luo, Steven Bai, Hong Tian and Mike Mikailov.

# 5. Summary

- The win ratio is conceptually simple and straightforward to apply and easy to calculate using WWR package in R and Win ratio Bootstrap.
- The win ratio method requires no assumption of data distribution
- The win ratio method has about the same power as Mann–Whitney test, logrank test and Cox model to detect the treatment difference.
- Win ratio method has been used in many trial reports in medical journals.
- We recommend the use of the win ratio method for analysing composite endpoints and non-normal data.

## References:


Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012 Jan;33(2):176-82.

Luo X, Tian H, Mohanty S and Tsai WY. An alternative approach to confidence interval estimation for the win ratio statistic. Biometrics. 2015; 71:139-145.

Bebu I and Lachin JM. Large sample inference for a win ratio analysis of a composite outcome based on prioritized components. Biostatistics. 2016; 17:178-87.

Wang D, Pocock S. A win ratio approach to comparing continuous non-normal outcomes in clinical trials. Pharm Stat. 2016; 15:238-45.

Junshan Qiu, Xiaodong Luo, Steven Bai, Hong Tian and Mike Mikailov. WWR: An R package for analyzing prioritized outcomes. Journal of Medical Statistics and Informatics. 2017; 5: