

# How is rescue medication defined, reported, and adjusted for in randomised controlled trials?

## A systematic review

Anca Chis Ster, Dr Victoria Cornelius, Dr Suzie Cro

### Objectives

- Estimate the proportion of articles that define and report the use of rescue medication.
- Evaluate the statistical methods used to adjust for rescue medication use on the primary outcome.
- Estimate the change in treatment effect after adjustment for rescue medication.

### Methods

- Phase II/III randomised controlled trials that evaluate the efficacy of a set of pre-established monoclonal antibodies in patients with chronic asthma or chronic eczema were eligible for this review.

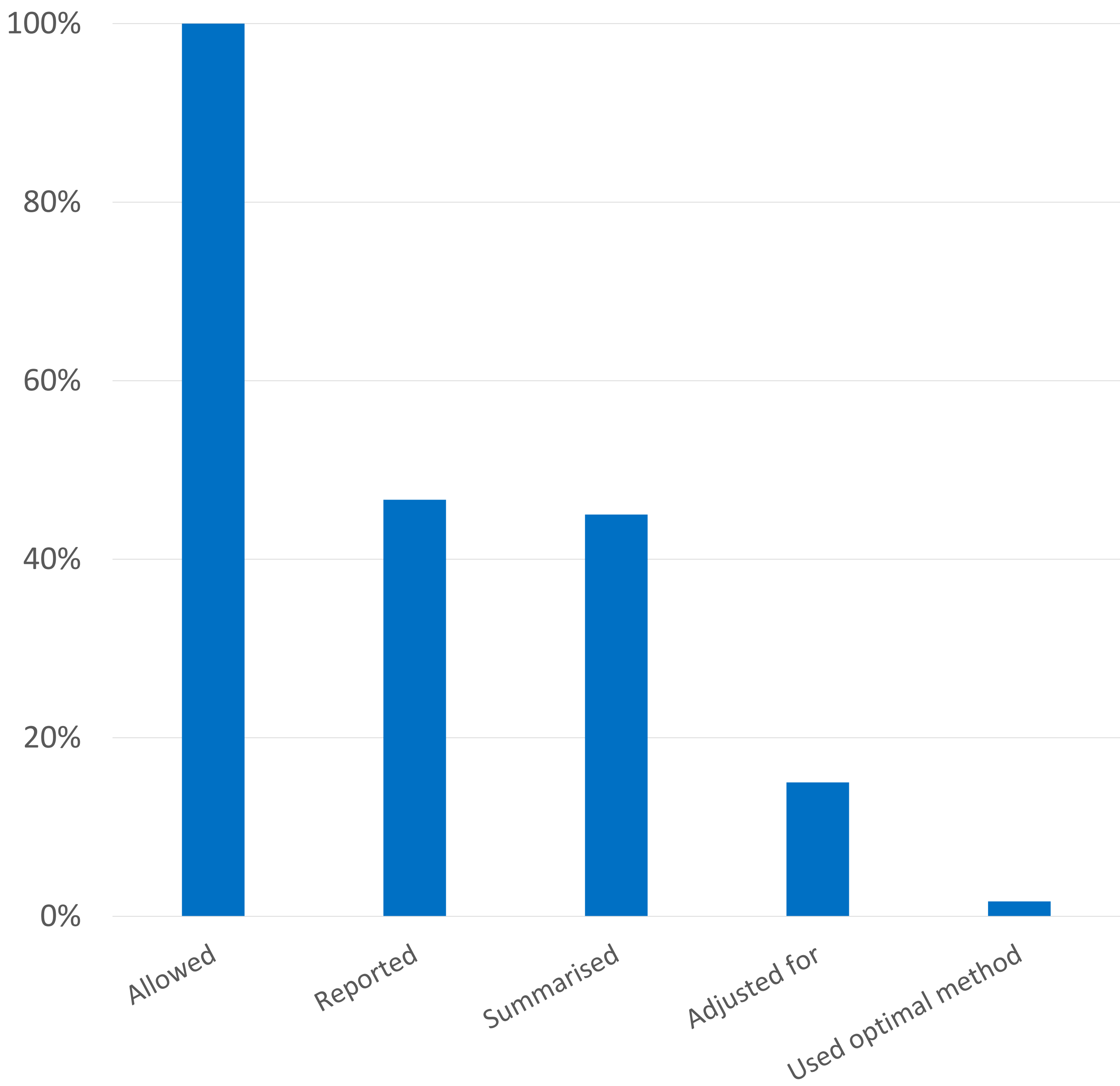
Scan the QR code for the full protocol :



### Results

- 60 RCTs were identified of which all allowed use of rescue medication in the trial.
- 28 reported rescue medication use in the primary publication; 27 summarised rescue use by arm.
- 9 trials undertook a rescue-adjusted analysis on the primary outcome.
- 1 trial used an optimal method of analysis.

Methods of rescue-adjusted analysis	N (%)
ANCOVA model setting efficacy data to missing after rescue medication use (or dropout) and LOCF method used to impute missing values	4 (44)
CMH test specifying participants as non-responders at rescue medication initiation (or study withdrawal)	4 (44)
Mixed model excluding assessments from the FAS if they were obtained at scheduled visits that were preceded by a limited subset of medications that could confound interpretation (Inc. rescue medication).	1 (11)
Total	9 (100)



### Conclusions

- Rescue medication is frequently permitted in trials but is not routinely reported.
- Despite evidence of imbalance in rescue use between arms, few articles showed interest in isolating the treatment effect in order to obtain rescue-adjusted treatment effect.
- Trials that did aim to obtain a rescue-adjusted treatment effect frequently employed methods that are highly vulnerable to introducing bias into the estimate.



# Controlled Multiple Imputation:

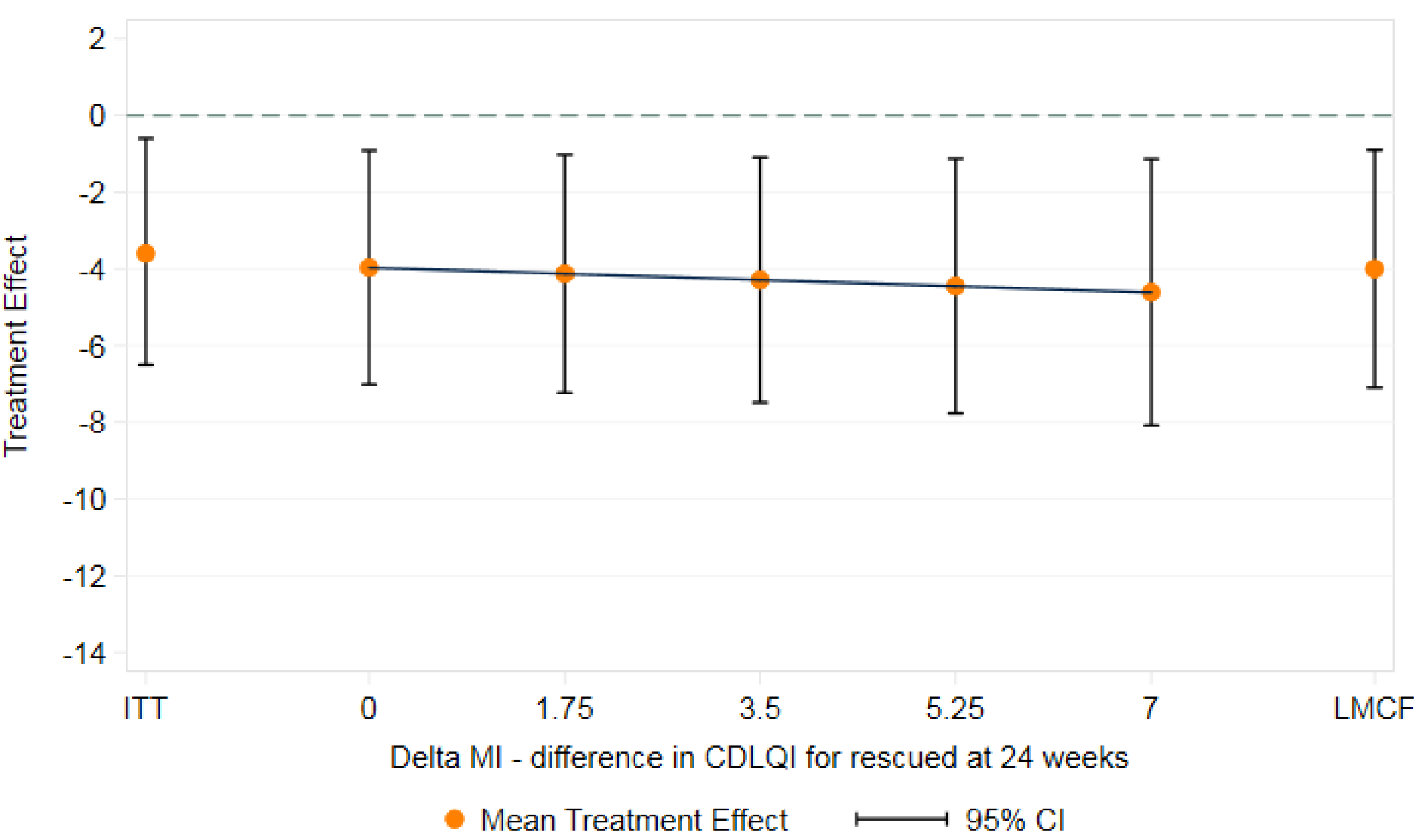
## An accessible tool for estimating hypothetical estimands in clinical trials

Suzie Cro, Susan Chan, Victoria Cornelius

### Introduction

- Intercurrent events in trials, such as use of rescue medication, are often unavoidable
- An Intention-to-treat analysis estimates the effect of the assigned treatment
- Estimating the treatment effect that would have been obtained if rescue medication had not been used may also be of value
- The ICH-E9 addendum discusses such ‘hypothetical’ estimands but does not provide guidance on estimation
- We demonstrate the use of controlled multiple imputation for estimating hypothetical estimands

### Results



- In all analyses a clinically significant treatment effect is obtained

### Methods

- An analysis of quality of life data (CDLQI) from the Atopic Dermatitis Anti-IgE Paediatric Trial
- Data post rescue is set missing and imputed using:

Controlled Multiple Imputation	Assumption
Delta-based	Rescued have mean outcome ranging from 0 to 7 points worse
Last mean carried forward	Rescued have mean of randomised arm at last time point prior to rescue

- Imputation performed using Stata command **mimix**
- Analysis model: Linear regression of 24 week CDLQI on treatment, baseline CDLQI, age and IgE
- Results are compared to an ITT analysis including all observed data post rescue initiation

### Discussion

- Anti-IgE is an effective treatment for severe atopic dermatitis in the absence of rescue medication
- Controlled multiple imputation provides a flexible accessible tool for estimating hypothetical estimands
- For more information on the mimix command see: <https://journals.sagepub.com/doi/10.1177/1536867X1601600211> or scan the QR code:





# AVATAR-AF: Getting to the heart of data management for analysis (5 simple rules to follow to ensure data integrity)

Nicholas A Johnson, Dr Thiagarajah Sasikaran

HELP! The last patient visit is scheduled for next week yet the team want the data cleaned, the database locked and the analysis completed and verified for abstract submission in 50 days.



We break for Christmas in 3 weeks...What do I do Stats Cat??!  
Do not fret, humble statistician!

Just follow these **FIVE SIMPLE RULES**

And remember...

**COMMUNICATION IS AT THE HEART OF GOOD DATA**



**MANAGEMENT**

## 2. Forge positive relationships with study centres

- Has a positive effect on recruitment
- Potentially reduces data entry errors
- Reduces time to resolve data queries
- Removes the risk of emails being lost and unanswered due to staff leave/turnaround

It **allows the site to feel like an integral part of the study:**

## 1. Embrace efficient database design

There is always a desire to ensure that as much information is collected as possible. However, it is also important to ensure that each piece of data has a valid reason for being recorded. **Quality, not quantity is key!**

## 3. Plan ahead! Schedule & include milestones

Discuss publication and conference plans early with your chief investigator!

Milestones may include:

1. Data cleaning of xx% patients
2. Last patient visit
3. Data cleaning of all patients
4. Hard/final lock of data base
5. Completion of analysis for abstract
6. Validation of analysis results for abstract
7. Checking of abstract draft

**COMMUNICATION**



## 4. Utilise time with the DSMB (and TSC) to discuss issues

If you have a DMEC/DSMB within your trial, treat this as an opportunity to raise queries. If something unexpected is happening within the trial data, do not be afraid to raise this to ensure **any issues can be resolved before it escalates into something more serious.**

## 5. Don't be afraid to escalate unexpected events

In working within clinical trials you are surrounded by **colleagues with a wealth of experience and information.** These institutions have structures which allow you to escalate difficult queries which may require input at a higher/senior level. Take advantage of this to ensure that the situation will not return when you no longer have time to find a solution.

### HOW WE USED THE RULES WITHIN AVATAR-AF

#### Plan ahead! Schedule & include milestones

Three pieces of information allowed us to submit at EHRA 2019:

- Deadline for abstracts was **08 Jan 2019**
- Database was locked on **26 Nov 2018**
- The plan to submit to EHRA was agreed in Spring 2018

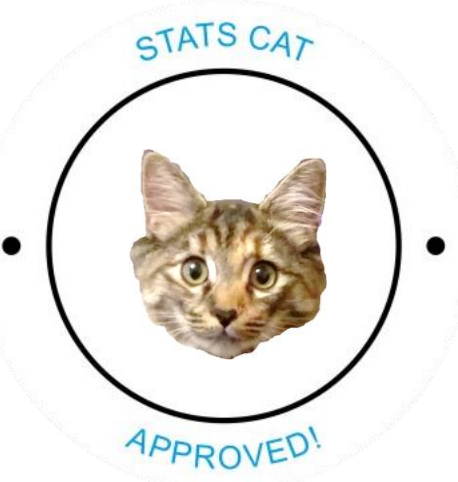
The final point allowed us to schedule routine, fortnightly data meetings over the summer. This ensured that data cleaning post final subject visit was minimal thus vastly reducing the time to final database lock.

#### Forge positive relationships with study centres

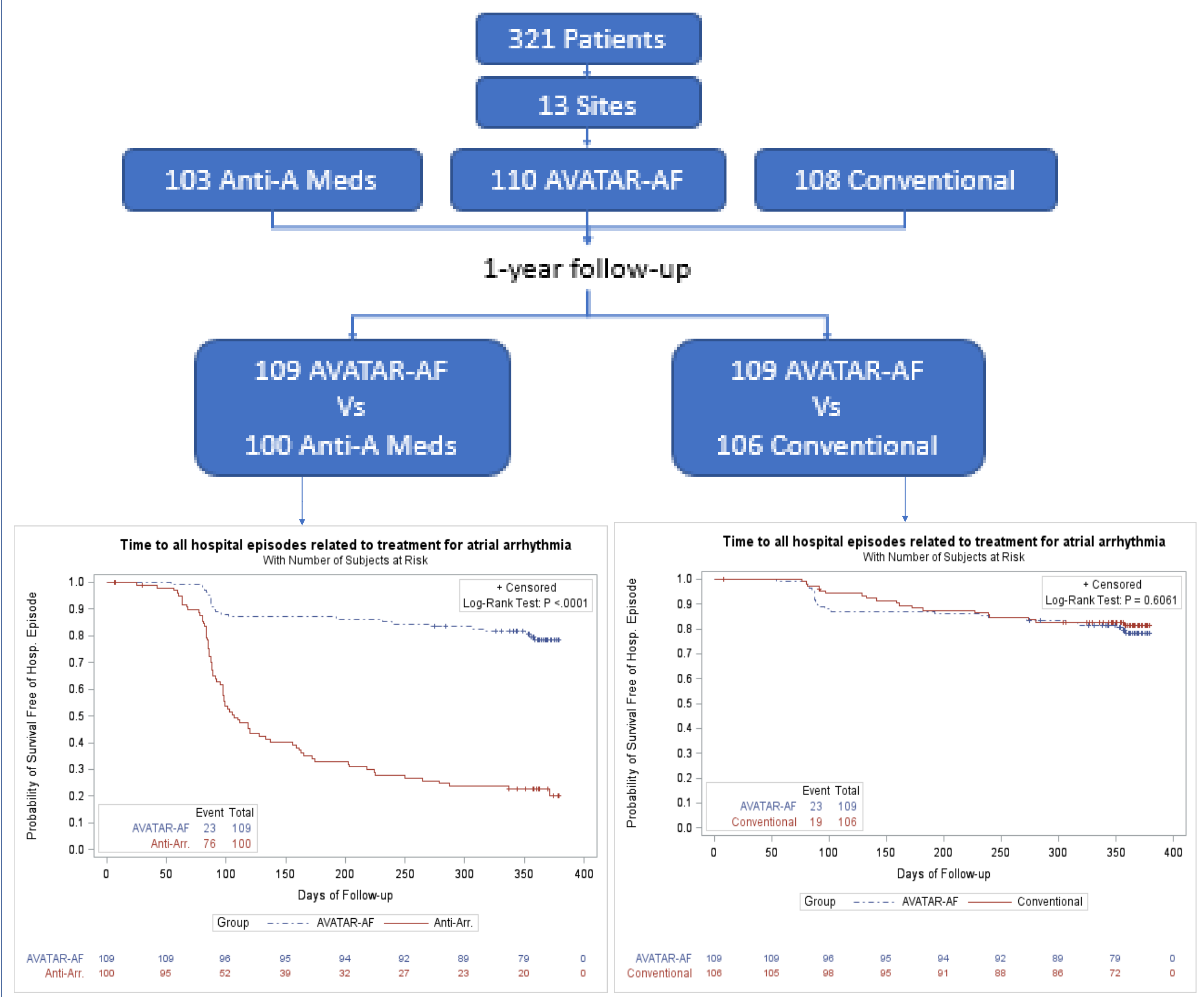
The AVATAR-AF trial held regular investigator meetings which allowed representatives from each site to meet up alongside the study team to discuss trial progress and issues in a relatively informal setting. This had a very positive effect on all of the sites such that by completion, every site stated they were willing to work with the CI again. Likewise, data queries were completed regularly and on time.

#### Utilise time with the DSMB to discuss issues

The AVATAR-AF DSMB met approximately every 6 months. One issue soon became apparent - the event rate in the AVATAR arm was lower than expected. This was potentially an issue and questions regarding power and increasing sample size were soon raised. In noticing this situation early we were able to monitor the situation over many meetings. It was agreed that as the primary analysis between AVATAR and anti-arrhythmic drug arms would not be negatively affected the decision was made to proceed as planned.



### AVATAR-AF – A brief guide





# Opportunities and experiences of accessing individual patient data for statistical research

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## Opportunities

Open access, individual patient data (IPD) provides statisticians and trialists the opportunity to undertake methodological research and reanalysis of clinical trials including IPD meta-analysis.

**2013**

EMA released a draft policy on publication & access to clinical-trial data including IPD

**2014**

The pharmaceutical industry committed to share IPD from clinical trials in the US/EU with scientific & medical researchers

**2019**

Many funders now mandate open access to IPD on completion of the primary research

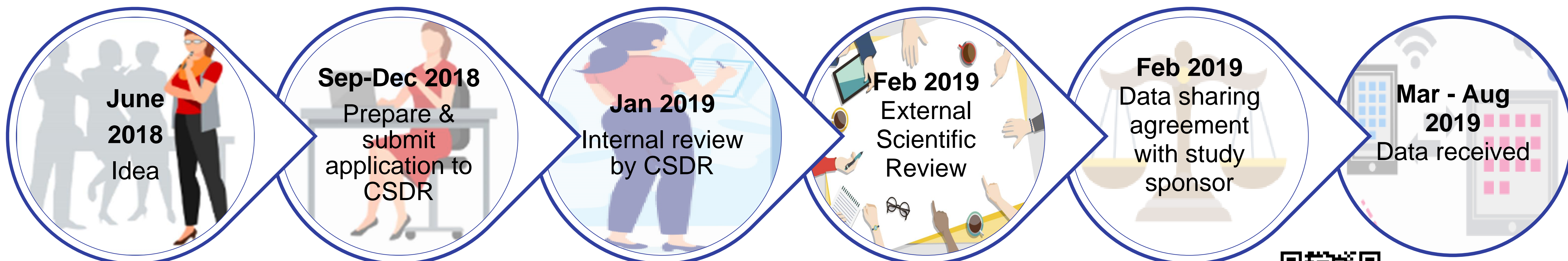
## What's available and where can you find it

IPD from completed clinical trials conducted by sponsors such as GSK and Roche and funders such as MRC and Wellcome can be accessed from:

- **CSDR** <https://clinicalstudydatarequest.com/Default.aspx>
- **Vivli** <https://vivli.org/>
- **YODA** <https://yoda.yale.edu/>

## Our experience

We wanted to investigate model based approaches for the analysis of adverse events using clinical trial data.



We found the experience to be a fast and efficient way to obtain valuable datasets for statistical research. To find out more about our project visit:



## Top tips

- Make sure the trial(s) have the data you need to answer your question:
  - Contact the sponsor's data sharing team – they can and are happy to help
- 'Analysis data-sets' are ready to use but are not available for all trials:
  - Request 'analysis data-sets' over 'raw data-sets' if possible
- Make contact with your institutions legal and ICT teams:
  - They can help with the data sharing agreement
- Identify where you will store the data, which members of your team will need access and how you will restrict access
- Access to data comes with strict conditions e.g. notification of any publications:
  - Make sure you are willing and able to comply