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Transparent reporting of adaptive clinical trials using concurrently randomised cohorts

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ABSTRACT

Adaptive clinical trials have designs that evolve over time because of changes to treatments or changes to the chance that participants will receive these treatments. These changes might introduce confounding that biases crude comparisons of the treatment arms and makes the results from standard reporting methods difficult to interpret for adaptive trials. To deal with this shortcoming, a reporting framework for adaptive trials was developed based on concurrently randomised cohort reporting. A concurrently randomised cohort is a subgroup of participants who all had the same treatments available and the same chance of receiving these treatments. The reporting of pre-randomisation characteristics and post-randomisation outcomes for each concurrently randomised cohort in the study is recommended. This approach provides a transparent and unbiased display of the degree of baseline balance and the randomised treatment comparisons for adaptive trials. The key concepts, terminology, and recommendations underlying concurrently randomised cohort reporting are presented, and its routine use in adaptive trial reporting is advocated.

KEY MESSAGES

- ⇒ Adaptive clinical trials have designs that change over time which makes treatment comparisons susceptible to confounding and bias if time trends in the level of background risk exist
- ⇒ A concurrently randomised cohort is a subgroup of participants in an adaptive trial who all had the same treatments available and were assigned to these treatments in the same way
- ⇒ Reporting of results for each concurrently randomised cohort within an adaptive trial transparently displays randomised comparisons, enabling an unbiased assessment of baseline balance and causal treatment effects
- ⇒ A concurrently randomised cohort reporting framework is recommended as a standard supplement to the planned primary analysis of adaptive clinical trials

Introduction

In fixed design clinical trials, the treatments being compared and the way participants are assigned to these treatments are unchanged. In adaptive clinical trials, these design features can change in response to the observed data or to external factors. These changes include adding new treatments or discontinuing underperforming treatments, as well as changing the chance that participants will be assigned to a particular treatment.[1 2] Participants in an adaptive trial might therefore have different treatments available to them and might have different chances of receiving these treatments. Adaptive designs, therefore, can be more flexible than fixed designs, but the data might be more difficult to interpret and report.

Assigning treatments by randomisation is a key feature of the design of clinical trials for both fixed and adaptive designs. Randomisation facilitates a causal interpretation for any differences in outcomes between the treatment groups. Thus one of the most important aspects of reporting the results of a randomised clinical trial is the transparent presentation of results by randomised treatment group.[3] This reporting includes both pre-randomisation characteristics to assess baseline balance and post-randomisation outcomes to assess causal treatment effects.

The changing design in an adaptive trial creates problems for the reporting of results by randomised treatment group. When participants have different treatments available or have different chances of being assigned to the available treatments, confounding might exist between treatments and the level of background risk, making crude treatment comparisons potentially biased.[4 5] For example, if background risk reduces over time and the chance of being assigned to a particular treatment increases over time relative to control, then crude treatment comparisons will be biased in favour of that treatment because relatively more low risk participants will be assigned to that treatment.

Specialised analysis techniques can adjust for confounding, including adjustment for calendar time, bayesian hierarchical modelling, information borrowing, indirect treatment comparisons, and many others.[1 2 6 7] The complexity of such methods, however, means that treatment comparisons are often presented in an opaque black box format. Here, we argue that, regardless of the primary analysis method, all adaptive trials should also report results by randomised treatment group in a transparent way. Reporting these additional results is not straightforward and a guiding framework for doing so is presented here. Our goal is not to give a prescriptive reporting checklist, but rather to introduce fundamental concepts that provide a foundation for reporting adaptive trials. The framework is built around the concept of a concurrently randomised cohort, a subgroup of participants in an adaptive trial who underwent the same randomised design. To

precisely define a concurrently randomised cohort, we first need to describe three key concepts for adaptive trials.

Stages of an adaptive trial

The first key concept is a stage within an adaptive trial, a time period between design adaptations where the study design is fixed. A new stage begins when a new treatment is added or an existing treatment is discontinued. Modifications to the available treatments, however, are not the only adaptations that define the start of a new stage in an adaptive trial. Modification of the randomisation probabilities is a common feature of adaptive trials (eg, to progressively favour the most promising treatment). This type of adaptation is known as response adaptive randomisation and involves a change in design without changing the treatments being studied.[8] Other changes can also define the start of a new stage, such as changing the randomisation stratification factors. In summary, any change to the treatments being compared, or the way in which participants are assigned to these treatments, is an adaptation that defines the start of a new stage.

The stages in an adaptive trial define the periods where the design of the trial is fixed. Fixed designs do not have temporal confounding; temporal confounding can exist in adaptive designs. Therefore, the distinct stages of an adaptive trial provide a basis for reporting results by randomised treatment group because unbiased treatment comparisons without temporal confounding are presented. Throughout this paper, when we refer to confounding, we are referring to the temporal confounding of comparative treatment effects that might occur as a result of the adaptive design.

Case study

Throughout this paper, we will use the Australasian Covid-19 Trial (ASCOT, ClinicalTrials.gov NCT04483960; Australian New Zealand Clinical Trials Registry ACTRN12620000445976) as a case study. ASCOT is an adaptive platform study of treatments for non-critically ill patients admitted to hospital with covid-19. The trial included treatment comparisons for multiple therapeutic domains. Here we discuss only the anticoagulation domain: three doses of heparin (low, intermediate, and therapeutic) and the combination of low dose heparin and aspirin. The primary endpoint was death, or new respiratory or vasopressor or inotropic support at 28 days. Full details of the results of the ASCOT anticoagulation domain are reported elsewhere.[9]

The anticoagulation domain of ASCOT was started in February 2021, with low dose heparin, intermediate dose heparin, and low dose heparin plus aspirin available for randomisation. A design adaptation occurred in September 2021 when the aspirin combination was dropped and a therapeutic dose heparin arm was added. The anticoagulation domain closed in April 2022. Depending on site of enrolment and other eligibility criteria, not all treatments were available to all participants. This design adaptation meant that some participants had three treatment options available whereas others had only two options available. In all cases, balanced randomisation to the available treatments was used without stratification. Figure 1 shows a schematic representation of the trial design. The periods before and after September 2021 define two stages where the study design was fixed. In each stage, however, two fixed randomisation schemes were available, one of which was common to both stages, giving three schemes overall. A total of 1574 participants were randomised to the anticoagulation domain, 18 of whom subsequently withdrew consent, and the remaining 1556 participants, the full cohort,[9] were divided between the three randomisation schemes (figure 1).

Participant randomisation scheme

As well as identifying the stages of an adaptive trial, we also need key information that defines the designs that were used in each stage. This approach

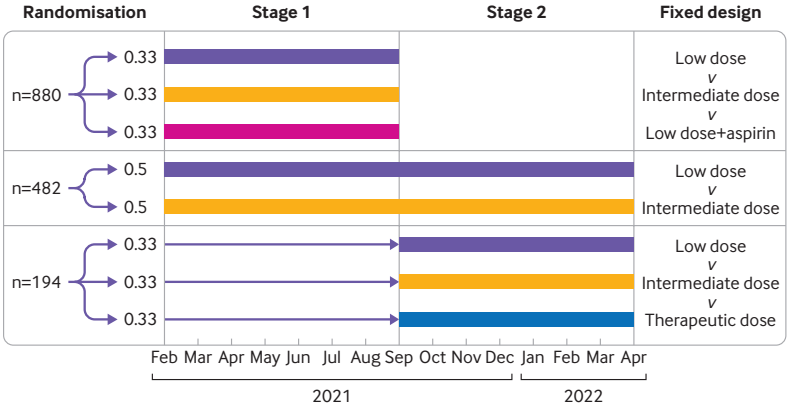

Figure 1 | Schematic representation of fixed designs within the overall adaptive design of Australasian Covid-19 Trial (ASCOT). In the overall adaptive design, 1556 participants were randomised to one of four anticoagulation treatments for covid-19, within one of three embedded fixed designs

requires precise documentation of the randomisation scheme that applied to individual participants. The second key concept required to define a concurrently randomised cohort is the participant randomisation scheme. Unlike a trial with a fixed design, where all participants are randomised under the same randomisation scheme, participants in adaptive trials are randomised under potentially different schemes (figure 1). For the purpose of presenting transparent randomised comparisons, documenting the precise randomisation scheme for each participant is important. This method involves documenting, for individual participants, the treatments that were available to that participant and the way in which they were assigned to one of these treatments. This information is captured in the participant randomisation scheme, a key data table necessary for valid interpretation of adaptive trials.

The participant randomisation scheme is a two way data table with each record (row) corresponding to a different study participant. The fields (columns) of the participant randomisation scheme capture the stage, randomisation probabilities, and any stratification factors that produced each participant's treatment assignment in the trial. Specifically, the participant randomisation scheme has one field corresponding to each separate treatment to which any participant was randomised during the trial. Also, the participant randomisation scheme has one field corresponding to each stratification factor that was used for any randomisation during the trial. In the participant randomisation scheme table, the randomisation probability that was used for each treatment is recorded for each individual, within the relevant treatment field. Some of these probabilities might be zero, where a treatment was not available to an individual. Also, a logical indicator is provided for each stratification field, specifying whether the randomisation for that individual was stratified by the relevant stratification factor.

Some adaptive trials, particularly platform trials, can have multiple therapeutic domains that separately assess different treatment classes and effectively operate as separate substudies. For example, the anticoagulation domain of ASCOT (figure 1) also had an antiviral domain. Each of these domains has its own treatments and randomisation scheme, which means that each domain has its own participant randomisation scheme. Furthermore, adaptive trials with multiple domains typically allow participation in one or multiple domains, and randomisation within a specific domain might be stratified by participation in other domains. This approach would mean that, in addition to stratification factors such as centre and prognostic variables, each domain's participant randomisation scheme would need to reflect stratification by other domains in the study.

The participant randomisation scheme is an individual participant listing and therefore would not typically be reported. Nonetheless, summaries of the participant randomisation scheme (eg, figure 1) are informative and the scheme is a key element of the individual participant data of an adaptive trial. The participant randomisation scheme is therefore integral to any data sharing arrangements. Specifically, when the individual participant data from an adaptive trial are made available, the participant randomisation scheme should be included in the individual participant data. We next show how the participant randomisation scheme determines each of the fixed designs embedded within an adaptive trial.

Embedded fixed designs

Each unique randomisation configuration within the participant randomisation scheme defines an embedded fixed design, the third key concept required to define a concurrently randomised cohort. We might think of an embedded fixed design as a fixed design trial that is embedded in the overall adaptive trial. Thus an embedded fixed design provides a subset of data without the temporal confounding that might exist in the overall adaptive trial. Each adaptive trial will have multiple embedded fixed designs, and these embedded fixed designs are both mutually exclusive and exhaustive. In other words, all participants within an adaptive trial belong to one, and only one, embedded fixed design. The subgroup of participants in the same embedded fixed design all had the same treatment options available to them, and were assigned to one of these options with the same randomisation probabilities and stratification factors.

One embedded fixed design can span multiple stages of an adaptive trial. If referring to an embedded fixed design restricted to a specific stage is required, we propose the qualification contemporaneous embedded fixed design, which includes only those participants randomised under the same embedded fixed design in the same stage. As we will discuss in the next section, reporting will usually use each embedded fixed design combined over all stages, but in some contexts, making use of each contemporaneous embedded fixed design might be advantageous.

Also, the same active treatment regimen can be present in multiple embedded fixed designs. The different characteristics of each embedded fixed design might therefore affect the performance of that treatment within each embedded fixed design. For example, platform trials commonly use matched placebos for individual active treatments, so different embedded fixed designs might involve administration of different placebos. This or other differences between embedded fixed designs might affect the performance of active treatments, which highlights the importance of understanding the different fixed designs that are embedded in the overall adaptive design.

Case study

For ASCOT, the right hand column of figure 1 specifies the embedded fixed designs that constitute the adaptive design; 1556 participants were allocated to one of three unique embedded fixed designs (ie, n=880, n=482, and n=194 participants). Two of the embedded fixed designs were restricted to one stage, whereas one of the embedded fixed designs extended across both stages. This example shows that there were four contemporaneous embedded fixed designs in total. The low dose versus intermediate dose design occurred in stage 1 because some sites did not offer aspirin and some participants were not eligible for aspirin.

Figure 1 also shows that the comparison between low dose and intermediate dose anticoagulation occurred in every embedded fixed design, illustrating that the complete information available about a treatment comparison might be the aggregation of information from multiple embedded fixed designs. This finding has a strong analogy with a meta-analysis, which involves aggregation of randomised treatment comparisons from multiple trials. Crude meta-analyses are generally considered to be biased if they are conducted by aggregating within treatment arms followed by comparison between treatments.[10] Instead, a meta-analysis must be conducted by first undertaking trial level randomised comparisons between treatments followed by aggregation of these randomised comparisons. The same principle applies for aggregating information about a treatment comparison that occurs in multiple embedded fixed designs of an adaptive trial. This principle is the primary motivation for the reporting framework that we now describe in detail.

Concurrently randomised cohorts

A subgroup of participants who share the same embedded fixed design is referred to as a concurrently randomised cohort. Each concurrently randomised cohort provides randomised evidence on causal treatment effects that is equivalent to a randomised study with a fixed design. We propose that adaptive trials provide concurrently randomised cohort reporting, which means that all concurrently randomised cohorts are identified and basic results are reported for each concurrently randomised cohort. This approach reflects the role of randomisation as a tool for causal interpretation of observed differences in treatment.

Pre-randomisation and post-randomisation information should be reported for each concurrently randomised cohort. Pre-randomisation participant characteristics should be presented by concurrently randomised cohort for each treatment arm to allow transparent assessment of baseline balance in randomised treatment comparisons. Post-randomisation outcomes should also be presented by concurrently randomised cohort for each treatment arm to provide a transparent display of information on causal treatment effects. The specific outcome information should be prespecified and depends on the outcome type, but might include event numbers for binary outcomes, means for continuous outcomes, or Kaplan-Meier estimates for time-to-event outcomes.

Case study

Table 1 shows baseline characteristics for the three concurrently randomised cohorts in ASCOT, along with those of the full cohort of 1556 participants. We found substantial imbalances in the characteristics of the full cohort which could lead to confounding in crude treatment comparisons. For example, across the four treatment arms, the prevalence of comorbidities ranged from 38% to 62%, those who had never smoked from 62% to 94%, those known to be vaccinated from 15% to 54%, and average age from 48 to 58 years. In contrast, baseline characteristics for each of the three concurrently randomised cohorts were more balanced and within the range expected due to chance variation associated with the randomisation schemes.

Table 2 shows the primary outcomes for the three concurrently randomised cohorts in ASCOT, along with those of the full study cohort. The relative risk for each treatment comparison is also shown, with low dose anticoagulation as the control arm. For the controlled comparison present in all three concurrently randomised cohorts (low dose *v* intermediate dose), concurrently randomised cohort reporting showed a relatively consistent treatment effect across the three cohorts (relative risks 0.76, 0.70, and 0.61, respectively). These values represent randomised treatment comparisons which pool to a relative risk of 0.71 in the full cohort.

For the two other controlled comparisons present in only one concurrently randomised cohort (low dose *v* low dose plus aspirin in concurrently randomised cohort 1 and low dose *v* therapeutic dose in concurrently randomised cohort 3), confounding was possible, originating from the baseline imbalances (table 1). In particular, concurrently randomised cohort 3 was a higher risk population than concurrently randomised cohort 2, which might mean that the pooled relative risk for low dose versus therapeutic dose in the full cohort is more extreme than the same relative risk in concurrently randomised cohort 3 (relative risk 1.84 *v* 2.44 for low dose *v* therapeutic dose). This finding indicates a possible confounding effect caused by the low risk concurrently randomised cohort 2, reducing risk on control but not on therapeutic dose in the full cohort. Reporting of outcomes by concurrently randomised cohort gives a clear picture of this effect, supplementing the model based primary analysis of the whole study cohort. This example illustrates that differences might exist between cohorts randomised

Table 1 | Baseline characteristics of Australasian Covid-19 Trial (ASCOT) for three concurrently randomised cohorts and full cohort of 1556 participants, in the anticoagulation domain*

	Embedded fixed designs (concurrently randomised cohort)								Adaptive design (full cohort)			
	Cohort 1			Cohort 2		Cohort 3						
Baseline characteristics	Low dose	Intermediate dose	Low dose+aspirin	Low dose	Intermediate dose	Low dose	Intermediate dose	Therapeutic dose	Low dose	Intermediate dose	Low dose+aspirin	Therapeutic dose
No of participants randomised	299	298	283	232	250	79	65	50	610	613	283	50
Mean age (years)	48	47	50	47	48	54	52	58	48	48	50	58
Sex												
Men	59	65	55	61	63	48	54	50	58	63	55	50
Women	41	35	45	39	37	52	46	50	42	37	45	50
Country												
India	92	94	97	92	92	8	12	8	81	84	97	8
Australia	7	6	2	7	8	14	34	22	8	10	2	22
Nepal	0	0	0	0	0	71	48	62	9	5	0	62
New Zealand	1	1	0	1	0	8	6	8	2	1	0	8
Median weight (kg)	68	69	68	69	70	68	74	66	68	70	68	66
Vaccination status												
Yes	15	16	15	43	52	57	66	54	31	36	15	54
No	75	77	75	57	48	43	34	46	64	61	75	46
Unknown	10	7	10	0	0	0	0	0	5	4	10	0
Smoking status												
Current	2	2	1	2	2	10	12	10	3	3	1	10
Former	7	4	5	9	10	38	23	28	12	9	5	28
Never	91	94	94	89	87	52	65	62	85	88	94	62
Comorbidities												
Yes	39	34	41	38	39	53	57	62	40	38	41	62
No	61	66	59	62	61	47	43	38	60	62	59	38

Values are % unless indicated otherwise.

*Anticoagulation domain: three doses of heparin (low, intermediate, and therapeutic) and combination of low dose heparin and aspirin.

Table 2 | Primary outcome results of Australasian Covid-19 Trial (ASCOT) for three concurrently randomised cohorts and full cohort of 1556 participants, in the anticoagulation domain*

Cohort	No of events	No of participants	Risk (%)	Relative risk (95% CI)
Concurrently randomised cohort 1				
Low dose	21	299	7.00	1
Intermediate dose	16	298	5.40	0.76 (0.41 to 1.43)
Low dose+aspirin	20	283	7.10	1.01 (0.56 to 1.82)
Total	57	880	6.50	—
Concurrently randomised cohort 2				
Low dose	8	232	3.40	1
Intermediate dose	6	250	2.40	0.70 (0.25 to 1.98)
Total	14	482	2.90	—
Concurrently randomised cohort 3				
Low dose	6	79	7.60	1
Intermediate dose	3	65	4.60	0.61 (0.16 to 2.34)
Therapeutic dose	7	50	14.00	1.84 (0.66 to 5.17)
Total	16	194	8.20	—
—Full cohort				
Low dose	35	610	5.70	1
Intermediate dose	25	613	4.10	0.71 (0.43 to 1.17)
Low dose+aspirin	20	283	7.10	1.23 (0.72 to 2.09)
Therapeutic dose	7	50	14.00	2.44 (1.14 to 5.21)
Total	87	1556	5.60	—

CI=confidence interval.
*Anticoagulation domain: three doses of heparin (low, intermediate, and therapeutic) and combination of low dose heparin and aspirin.

at the same time but within different concurrently randomised cohorts.

Tables 1 and 2 present the essentials of concurrently randomised cohort reporting, and might be viewed as implementing existing standards for reporting baseline and outcome data, as described in items 15-17 of the Adaptive designs CONSORT (Consolidated Standards Of Reporting Trials) Extension (ACE) checklist,[11] but with the added enhancement that the reporting is specific to concurrently randomised cohorts. The full cohort results in table 2 are based on simple pooling of all concurrently randomised cohorts. Any attempt to infer causal effects from these results will be biased by time dependent differences in the baseline risk of the outcome between treatment arms observed in the full cohort (table 1). In general, results for the full cohort based on simple pooling in an adaptive trial should not be used for treatment comparisons. Treatment comparisons should be based on analyses that appropriately account for temporal changes in the baseline risk of the outcome supplemented by randomised results specific to concurrently randomised cohorts, such as those in table 2.

Previously we introduced the term contemporaneous for describing an embedded fixed design where all participants were randomised within the same stage. The same term can also be applied to concurrently randomised cohorts that span multiple stages, such as concurrently randomised cohort 2 in tables 1 and 2 (ie, a contemporaneous concurrently randomised cohort is a concurrently randomised cohort where all participants were randomised during the same stage). For the case study, underlying concurrently randomised cohort 2 are two contemporaneous concurrently randomised cohorts, each with a concurrent cohort randomised to low dose or intermediate dose anticoagulation. Combining contemporaneous concurrently randomised cohorts into one concurrently randomised cohort for reporting purposes validly preserves the randomisation and the causal interpretation of the randomised treatment comparisons, which justifies the way we presented the information in tables 1 and 2. Nonetheless, in some circumstances, particularly when a study is conducted over many years, separate reporting of contemporaneous concurrently randomised cohorts might be useful to explore changes in the effect of treatment over time. The distinction between contemporaneous, meaning within the same stage, and concurrent, meaning within the same fixed design, is an important conceptual distinction for adaptive trials.

Aggregated summaries

The primary analysis for an adaptive trial will effectively provide a mechanism for synthesising the randomised information from each concurrently randomised cohort into a valid combined estimate of the treatment effect. Depending on the complexity of the primary analysis, this process could be limited to the synthesis of direct randomised treatment comparisons only, such as those in table 2, or could also involve the synthesis of indirect non-randomised treatment comparisons. Indirect treatment comparisons from adaptive trials are sometimes referred to as comparisons with non-concurrent controls.[6 12]

Together with a modelled primary analysis, having a more transparent display of aggregated summaries based on straightforward averages of the treatment comparisons from each concurrently randomised cohort, is also useful. The methods for providing these aggregated summaries are based on repurposing of network meta-analysis methodology and have been described elsewhere.[7] These aggregated summaries are not intended to replace the primary model based analysis, which remains the primary inferential tool and the mechanism by which valid inference is ensured, such as the control of type I errors. Nonetheless, aggregated summaries are a useful supplement to the primary analysis because

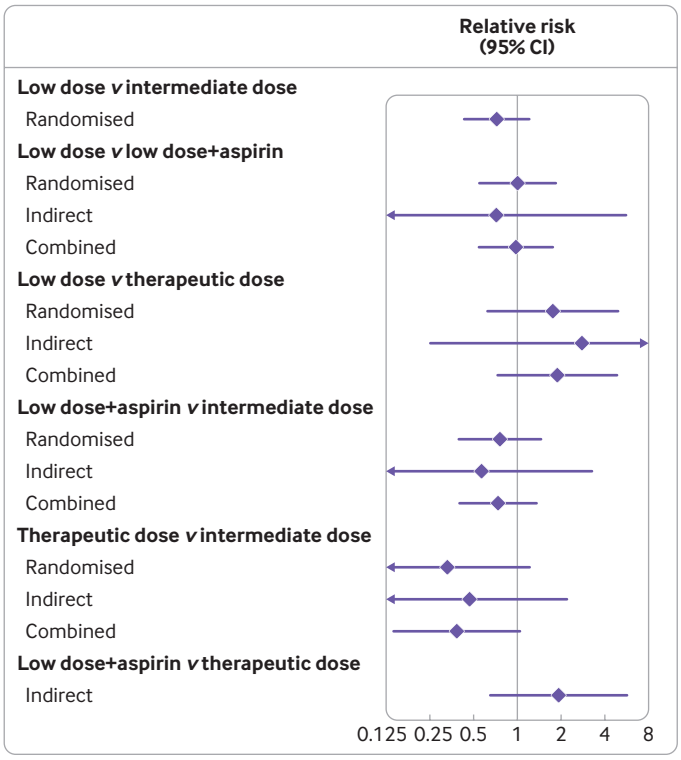

Figure 2 | Aggregated summaries of all treatment comparisons in Australasian Covid-19 Trial (ASCOT) based on randomised, indirect, and combined evidence. Treatments are low dose anticoagulation alone or in combination with aspirin, intermediate dose anticoagulation, and therapeutic dose anticoagulation. Relative risks >1 favour the first treatment

they provide a transparent display of the direct randomised evidence, the indirect non-randomised evidence, and the combination of the two.

Case study

Various indirect comparisons are available in ASCOT. For example, the low dose plus aspirin arm and the low dose control arm can be indirectly compared by assessing these two arms from concurrently randomised cohorts 1 and 2, respectively, with the intermediate dose arm as a common reference comparator. This indirect comparison is based on a non-concurrent control arm and might provide useful additional information beyond the randomised controlled comparison available from concurrently randomised cohort 1.

Figure 2 provides an aggregated summary of all randomised, indirect, and combined evidence for each of the six treatment comparisons available within ASCOT, based on the concurrently randomised cohort specific outcomes reported in table 2. For one comparison, all evidence was randomised (low dose *v* intermediate dose), and for one comparison all evidence was indirect (low dose plus aspirin *v* therapeutic dose). For all other comparisons, the available evidence was a combination of randomised and indirect comparisons. The indirect evidence was generally consistent with the randomised evidence, but in all cases the indirect evidence added little information to the randomised evidence.

The primary analysis for the ASCOT anticoagulation domain used a bayesian hierarchical model.[9] This model can incorporate information borrowing from non-concurrent controls as well as adjustment for secular trends and patient characteristics. The aggregated summaries in figure 2 supplement the model based primary analysis by providing a transparent display of the breakdown between concurrent and non-concurrent comparisons, as well as the combination of the two. Although the primary model based analysis has the advantage of efficiently extracting maximal information from the data, the aggregated summaries in figure 2 and the concurrently randomised cohort reporting in table 2 supplement the modelled analysis by providing an accessible display of the randomised and non-randomised contributions to the primary analysis. These aggregated summaries do not replace the prespecified primary analysis and would be considered descriptive rather than inferential. Because of the potential for the primary analysis to be complex, however, a more transparent aggregated summary of the concurrently randomised cohort specific comparisons, as shown in figure 2, is a useful supplement to the primary analysis.

Discussion

Randomised trials should always report results by randomised treatment group to transparently display the available evidence on the causal treatment

BOX 1 | KEY TERMINOLOGY

Adaptation: change to available treatments or the way participants are assigned to treatments

Stage: time period between adaptations when the design is fixed

Participant randomisation scheme: individual listing that captures, for each participant, the treatments that were available to them and their chance of receiving these treatments

Embedded fixed design: one of the unique randomisation configurations occurring within the participant randomisation scheme, which is equivalent to a fixed design embedded within the overall adaptive trial

Concurrently randomised cohort: cohort of participants who had the same treatments available and the same chance of receiving these treatments

Contemporaneous cohort: cohort of participants who were randomised within the same stage, although not necessarily within the same concurrently randomised cohort. Participants might be contemporaneous but not concurrent, and vice versa

BOX 2 | KEY RECOMMENDATIONS

All adaptive trials should report key results by concurrently randomised cohort, termed concurrently randomised cohort reporting, and have the following elements:

For transparent reporting of the randomised design, each embedded fixed design within an adaptive trial should be identified and reported. The elements of an embedded fixed design are the available treatment arms, randomisation probabilities for each treatment arm, and any factors used to stratify the randomisation. The collection of embedded fixed designs defines the available concurrently randomised cohorts.

For transparent reporting of baseline balance, key pre-randomisation characteristics and sample sizes should be reported by treatment arm for each concurrently randomised cohort.

For transparent reporting of randomised comparisons, post-randomisation outcomes should be reported by treatment arm for each concurrently randomised cohort. At a minimum, this reporting should include the primary outcome but might also include other efficacy or safety outcomes. Depending on the types of outcomes, this reporting could include event numbers for binary outcomes, mean changes for continuous outcomes, or Kaplan-Meier estimates for time-to-event outcomes.

For transparent data sharing, the participant randomisation scheme should be considered as an integral component of the individual participant data of an adaptive trial. The participant randomisation scheme should be made available as part of the individual participant data in any data sharing arrangements.

effects. This approach is a challenge for adaptive trials because crude treatment comparisons are not randomised evidence and might have confounding originating from changes in design during the study. Statistical models can be used to deal with this confounding, but the results of modelled analyses do not provide a clear summary of the core data underlying the randomised comparisons. This method prevents transparency and hinders the reuse of trial results by other researchers in systematic reviews and meta-analyses. Having guidance on the transparent display of core results from adaptive trials is therefore important.

We have introduced a framework for transparent reporting of results from adaptive clinical trials based on the fundamental concept of a concurrently randomised cohort, a cohort of participants that all had the same treatments available and were allocated to these treatments in the same way. We have presented this framework in the context of individually randomised parallel studies, the most common design used in adaptive trials. We have also introduced a range of terms that are useful additions and clarifications to the lexicon of adaptive trials. Box 1 provides a summary of the key terminology for describing our proposed reporting framework. This terminology includes a clear distinction between the concepts of concurrent and contemporaneous cohorts, the former denoting randomisation within the same embedded fixed design and the latter denoting randomisation within the same stage. Our reporting framework is motivated by concurrent randomisation being the primary basis for unbiased treatment comparisons.

Our primary recommendation is that all adaptive trials should provide concurrently randomised cohort reporting. This approach requires identification of the fixed designs that are embedded within the overall adaptive design and construction of all of the participant cohorts that were randomised under the same fixed design. Concurrently randomised cohort reporting then involves display of baseline characteristics and outcomes by treatment group for each of these cohorts. Box 2 summarises our key recommendations.

Guidelines for adaptive trials, including reporting standards, have previously been published.[11 13] These guidelines have not explicitly recommended concurrently randomised cohort reporting but have implicitly alluded to some of the problems that we have looked at more fully here. For example, the ACE checklist recommends that baseline characteristics should be reported by stage for each treatment

group.[11] Also recommended is that treatment effects should be reported from each stage of an adaptive trial.[7] Although these stage specific recommendations are influenced by the same principles that we examined here, an important distinction exists between reporting by stage and reporting by concurrently randomised cohort. This distinction comes from the difference between contemporaneous and concurrent participants (box 1). We believe that we have examined these questions in detail and we propose that our recommendations should be added to existing guidelines. In particular, we hope that future updates to the reporting standards in the ACE checklist and other guidelines can explicitly include the added requirement for concurrently randomised cohort reporting of adaptive trials.

We have avoided recommending primary analysis methods for adaptive trials, which will often involve complex analytical techniques.[14 15] Bayesian and frequentist statistical models are common and valid for primary analyses.[16–18] Furthermore, the preferred approach to incorporating (or not incorporating) non-concurrent controls might differ from trial to trial.[6 7 12] We do not provide any general recommendations on these topics here. Regardless of the methodology used in the primary analysis, however, presenting transparent summaries of the available randomised evidence in an easily interpretable format is important. Concurrently randomised cohort reporting provides these summaries and should be considered standard practice in the reporting of adaptive clinical trials.

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Contributors ICM drafted the original version of the manuscript. All authors provided critical input, review, and revision for important intellectual content. All authors have been working for several years on the design, conduct, and interpretation of adaptive clinical trials, and provided either statistical or clinical expertise. ICM is the guarantor. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Patient and public involvement The ASCOT trial steering committee included a consumer representative who provided input to the study on behalf of patients and the public. No patients or public were requested to advise on the writing of the manuscript.

Ethics approval This study involves human participants and was approved by Melbourne Health Human Research Ethics Committee (HREC/62646/MH-2020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The Australasian Covid-19 Trial (ASCOT) international trials steering committee is open to collaborative agreements with other investigators and sponsors. These will be on a case-by-case basis but with a willingness to share infrastructure and data from ASCOT. Written agreements specifying aspects relating to collaborations will be entered into before commencement of collaborative trial activities.

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