The Critical Care Evidence Base that is Critical For Exams

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2024 Update: Dr Joshua Pillemer and Dr Karthik Venkatesh

Advice for the FCICM exam

1. You must know at least the key evidence that informs modern intensive care practice – don't worry about quoting the reference exactly but at least be able to quote the major findings and know the ***implications of the findings***.

2. You must know about the major multicentre RCTs that have led to Aust and NZ's international reputation for this sort of clinical research in the last two decades [Dopamine, SAFE, CHEST, NICE, RENAL, MERIT, ARISE, ADRENAL, TARGET, PLUS, POLAR, SPICE …], and know the strengths and weaknesses of these studies.

The ANZICS-CTG website is an excellent resource for seeing recently published and currently-active trials to remain up to date

3. You must also know about the major ANZ trials recently completed (eg SuDDICU, PATCH, TEAM) and important trials currently underway or about to start in your ICUs (ARISE-FLUIDS, BLING III, REVISE, MEGA-ROX, REMAP-CAP)

4. You must know about major current controversies, including synthetic colloids (Joachim Boldt scandal in HES research), steroids in sepsis / ARDS, different approaches to nutrition, management of HIE/OHCA, and now ECMO/ECLS. It is worth at least looking at the program of meetings such the ANZICS Clinical Trials Group ASM – many examiners will be there.

5. You must know the major international guidelines [Surviving Sepsis, Brain Trauma Foundation, International Liaison Committee on Resuscitation] and the strengths and weaknesses of these guidelines.

6. You must know at least the basics of 'how to sensibly evaluate a paper'. This includes as a minimum a working knowledge of how to assess ***internal and external validity***. The CONSORT (Consolidated Standards of Reporting Trials) statement will help you with internal validity (ie was the study well done). You must appraise external validity yourself ("how does this study apply to **MY** patient population in my environment") and understand how to rationally evaluate subgroups and secondary endpoints in the context of a large pragmatic trial. Also think about the validity of post hoc as opposed to preplanned analyses and why these can lead us astray.

7. My approach to a 'Critically Evaluate …..' question (often poorly done in the exam) is no different to how I write a protocol for my department. (1) Outline the issue, (2) Summarise the current evidence, including strengths and weaknesses, (3) Here is the bottom line, (4) Based on the above, this is what I recommend (5) So do what I say, please. Regardless of how strong or weak the evidence is you must ultimately have a statement of what YOU will do.

8. The EBM / statistics / clinical research questions in the written paper are a very good bet (there is almost always one there) and are basically designed to

test the question ‘have you been going to journal club’? ‘do you take an interest in the literature’? ‘do you stay up to date’? (not by reading UpToDate !!!!). You do NOT have to know how to evaluate complex statistics, but a general understanding of the principles is expected. There is one question like this in *every* written paper, so take the time to understand the basics.

9. Understand the basic principles of statistics in EBM:
    a. What factors determine the pre-planned sample size calculation?
    b. What is meant by the term statistical power?
    c. Have some understanding of the way we interpret the data/our trial design, and the advantages and disadvantages of each:
        i. Frequentist approach
        ii. Bayesian approach
        iii. Superiority vs non-inferiority studies and the rationale for each

Useful Resources

1. Critical Care Reviews (criticalcarereviews.com)
    a. This is an up-to-date resource and arguably the current best resource for dissemination of critical care literature
    b. Rob sends a weekly email with the newest and most relevant studies, including RCTs, SR-MAs, guideline updates, observational studies and useful narrative reviews
    c. Also includes a paper of the week that typically is very useful and topical, particularly as part of Part 2 preparation

2. The Bottom Line (thebottomline.org.uk)
    a. Fantastic summaries of landmark papers
    b. International contributors
    c. Has a dedicated “Intensive Care Medicine” section

3. Wellington ICU (@WellingtonICU)
    a. These guys have started a fantastic initiative where the papers being covered in their Journal Club are summarised in a series of punchy tweets on Twitter
    b. Again, a low-effort way to keep on top of things

4. The local internet sites [CritIQ www.critiq.com (great journal club) and Intensive Care Network ICN intensivecarenetwork.com]

5. Good information in blogs like LifeinTheFastLane (LITFL). The FOAMed stuff is growing exponentially, but ***beware the line where critique turns into opinion***

6. The JAMA User’s Guides to the Medical Literature. Links available from many sites or buy the book from AMPCo.

7. Fink M, Hayes M and Soni N (eds) *Classic Papers in Critical Care*, Bladon Medical Publishing. A collection of all those older papers which are really important and led to the development of how we now practice.

8. Iphone/Ipad app *ICU Trials*
    a. Relatively up to date – useful resource for highlighting some of the older studies that informed earlier practice – does miss some newer studies

What are the must-know topics in Intensive Care?

There are several domains that form essential knowledge in our practice, in particularly the syndromes and disorders that are specific to our scope of practice. Below are some key domains; this list is by no means exhaustive but hopefully will highlight some of the major trials that have been fundamental in developing intensive care practice.

1. **Fluid Resuscitation:**
   The key topics to cover in fluid resuscitation, which have generally been in the domains of sepsis resuscitation, or for general fluid use within the ICU.
   - Crystalloid vs Colloid?
   - Balanced crystalloid vs saline?
   - How much fluid?
   - What rate to give fluid?

a. Albumin vs saline:
   Start with The SAFE Study Investigators, A comparison of saline and albumin for fluid resuscitation in the intensive care unit, ***New Engl J Med*, 2004, 350: 2247-2256**. See also The SAFE Study Investigators, Saline or Albumin for Fluid Resuscitation in
   a. The substudies of SAFE are crucial, including the TBI subgroup analysis (hence why we don't use Albumin in acute brain injury)

   All this of course was prompted by Cochrane Injuries Group Albumin Reviewers, Human albumin administration in critically ill patients: systematic review of randomised controlled trials, ***BMJ*. 1998 Jul 25;317(7153):235-40**.
   – certainly the most controversial paper in intensive care in a long time, and the stimulus for SAFE.

b. Starches
   Starches are well and truly out of favour following the findings from the CHEST and 6S trials, both published in NEJM. Signal of increased mortality and increased requirement for renal replacement therapy in cohorts who received starch therapy.

   In addition: The most prolific researcher in the area has been convicted of academic fraud with over 80 papers (a large part of the HES literature!) retracted. Know about the HES controversy (Joachim Boldt).

c. Restrictive vs liberal fluids?
   FEAST (K. Maitland, ***New Engl J Med, 2011***) and work which has flowed from this which are likely to radically change fluid resuscitation practices in paediatrics.
   Recently in sepsis – the CLASSIC and CLOVERS trials (2023, both in NEJM), both of which did not show a significant difference in mortality between a liberal vs restrictive fluid strategy. A key discussion point here though is how fluid management in ICU over the years has evolved to a more restrictive fluid strategy anyway, so that the 'liberal' arms received less fluid than they would have if the trials were conducted 10-15 years earlier.

   ARISE-FLUIDS is an ANZICS-CTG study that is currently underway and aims to answer the question about early vasopressors vs. standard fluid resuscitation in the domain of septic shock.

   In the pancreatitis domain, the WATERFALL trial compared an aggressive vs more restrictive fluid resuscitation approach, and indicated that an aggressive fluid resuscitation strategy worsened fluid overload without any meaningful clinical benefit (NEJM 2022).

d. Type of crystalloid
This has been explored in several studies, based on the premise that the high chloride load in saline solutions may exert a nephrotoxic effect (Yunos, ***JAMA* 2012:308:1566-1572)**.

Key studies to know:
PLUS – ANZICS CTG study
SPLIT
SMART
SALTED
BaSICS (>10,000 patients), and looked at both fluid type and rate of administration

A recent SR-MA by Naomi Hammond has compiled the data: *Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis* **NEJM Evid 2022;1(2) DOI: 10.1056/EVIDoa2100010**

2. **Metabolic management**

a. Glycaemic control
Strict vs liberal glucose control in the ICU?
NICE-SUGAR was one of the landmark ANZICS-CTG studies demonstrating the potential harms associated with strict glycaemic control in the ICU *Intensive versus Conventional Glucose Control in Critically Ill Patients*, ***New Engl J Med*, 2009, 360:1283-1297**, a large pragmatic multicentre PRCT in response to van den Berghe G,Wouters P, Weekers F, *et al*, Intensive insulin therapy in critically ill patients.
***N Engl J Med*. 2001 Nov 8;345(19):1359-67**. Make sure you have thought about the pros and cons of IIT and the external validity of van den Berghe's paper.

There is increasing discussion about the validity of a one-size-fits all for glucose targets in the ICU, in particular how these apply to diabetic patients (NB that only 20% of the patients in NICE-SUGAR were diabetic).

b. Nutrition
Possibly one of the most confusing sections of the literature, with endless trials and no clear 'best method' when it comes to delivery of nutrition to our patients.

What are the key questions in nutrition?
- Enteral vs parenteral?
- Early vs delayed nutrition?
- Who may benefit from a hypercaloric nutrition strategy? (ie hypercatabolic patients → burns, severe trauma, pancreatitis)
- Does it matter whether we meet the caloric targets or not?

What are the key studies?
EPaNIC: Early (day 3) vs late (day 8) PN. Late → earlier ICU discharge, more likely to be discharged alive, no difference in mortality (hospital, 90 day).
Early PN: Early PN (day 0-1) vs standard care. No difference in 60 day mortality, less ventilation days in early PN group, no difference in complications. ***("PN is safe!")***
CALORIES: Early PN neither beneficial nor harmful compared to EN. EN gives more vomiting and hypoglycaemia, but no harm. Both groups under-fed.
TARGET: Targeting rate of 1mL/kg using either 1.5kcal/mL or 1kcal/mL feed. No difference in 90 day mortality, or any other outcomes.
- This is a high quality well-powered RCT, another from the ANZICS-CTG

PermiT: Permissive underfeeding (with full protein supplementation) is likely safe, but trial underpowered to detect survival benefit.

3. **Respiratory**

There are several domains to cover here, and this is one of the cornerstones of ICU practice.

- ARDS and the management of hypoxaemic respiratory failure
    - Ventilation strategies
    - Paralysis
    - Proning
    - Recruitment maneuvres
    - The role of VV-ECMO
    - Steroids and immunomodulation
    - Role of pulmonary vasodilators
- Ventilation / CO2 removal
- Airway management
    - Direct vs video laryngoscopy

ARDS:
ARDSNET, ***N Engl J Med*, 2000 May 4;342(18):1301-8.** Low volume ventilation improves survival in acute lung injury / ARDS. And see also the subsequent ARDSNet studies (ALVEOLI – Higher vs lower PEEP)., Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome, ***N Engl J Med*. 2004 Jul 22;351(4):327-36.**

Definitions for ARDS: **Berlin definition for ARDS (*JAMA, 2012, 307:2526)*.** This was the original definition, but a more recent study has updated parameters Matthay MA, Arabi Y, et al. **A New Global Definition of Acute Respiratory Distress Syndrome.** Am J Respir Crit Care Med. 2024 Jan.

Neuromuscular blockade:
The initial ACURASYS trial of cisatracurium, ***NEJM 2010, 363(12):1107)*** suggested benefit from paralysis in ARDS, but this has since been refuted by the more recent ROSE trial (***NEJM 2019*, 380:1997**). ROSE was a larger multicentre study compared to ACCURASYS, and used strategies more in keeping with usual practice (higher PEEP in both groups, lighter sedation in the control group). ROSE was stopped early due to futility.

Proning:
One of the most significant trials with regards to the magnitude of treatment benefit, the PROSEVA trial **(*NEJM 2013, 368(23):2159)***. This was an RCT of proning in patients with severe ARDS, with a significant survival benefit in the proning arm. NB the centres in the trial had >5 years experience in proning, which initially raised questions on external validity and concerns were raised about potential selection bias in the trial population. However after the recent COVID experience, proning is a much more familiar and recognised strategy in severe respiratory failure.

Recruitment maneuvres:
One phase 2 trial **(PHARLAP)** which compared conventional ventilation with 'lung protective ventilation' including staircase recruitment manouvres was terminated in 2017 in light of a large predominantly Brazilian trial (**ART trial, *JAMA* 2017***)*.

High frequency oscillatory ventilation:
Know about OSCILLATE and OSCAR (both ***New Engl J Med* 2013**) and know what they say (and do not say) about HFOV as both an early and as a rescue therapy.

ECMO in respiratory failure:
CESAR (Peek, ***Lancet* 2009**). And now, to keep the controversy going, we have the **EOLIA** trial (***NEJM, 2018)* –** have a think about the role of the DSMB in this trial and

whether it was appropriate to terminate it early. Several smaller studies have been released following the pandemic but CESAR and EOLIA remain the two larger RCTs.

Under the ECMO banner I would also include extracorporeal carbon dioxide removal (SUPERNOVA and REST), with the evidence not being in favour for ECCO2 at this point.

a. Other key topics in respiratory:

COVID-19:
Several studies have investigated immunomodulation as part of ARDS management in the setting of COVID-19

- RECOVERY
- REMAP-CAP
- COVID STEROID-2 trial
- Specific studies investigating tocilizumab, sarilumab

Corticosteroids have been investigated in influenza-induced ARDS, with a signal of increased harm in patients receiving steroids. This could be revisited following the success of steroids in COVID-19 illness

Pneumonia:

- Role of corticosteroids in severe pneumonia (recently published ESCAPe trial *Meduri et al.* **Intensive Care Medicine 2022**, CAPE-COD *Dequin et al* **NEJM 2023**), REMAP-CAP steroid arm continues underway
- Antimicrobial therapy and the role of procalcitonin as a biomarker for treatment duration

NIV in COPD:
Celikel ***Chest* 1998, 114:1636-42** or the classic study by Esteban ***NEJM* 1995**. Without doubt conscious COPD patients do better with non invasive facemask ventilation rather than endotracheal intubation. But don't use it in the wrong patient group: Estban A, Frutos-Vivos F, Ferguson ND, *et al*, Noninvasive Positive Pressure Ventilation for Respiratory Failure After Extubation, ***New Engl J Med*, 2004, 350:2452-2460.**

High flow vs NIV:
There is a huge amount of evidence surrounding the advantages and disadvantages of each modality in the management of respiratory failure

4. **Renal**

Key questions:
Dose of renal replacement therapy?
Timing of renal replacement therapy?

Key studies:

ANZICS CTG studies

- Low-dose dopamine in patients with early renal dysfunction: a placebo controlled randomised trial, ***Lancet*. 2000 Dec 23-30; 356(9248):2139-43.** Definitively puts this one to rest – the place for intravenous dopamine is in the medical museum.
- STARRT-AKI

Other key studies:

- The RENAL Study Investigators ***New Eng J Med,* 2009, 361:1627-1638.**
- Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial

- AKIKI & AKIKI 2 – timing of renal replacement therapy

5. **Septic shock**

Know the Surviving Sepsis Campaign Guidelines, how the evidence is generated and the pros/cons of these guidelines and how they influence your practice.
Understand the evolving definitions of sepsis and septic shock and how this changes the interpretation of trial data over the years. In light of the definitions of sepsis, the unknown disease biology and the challenges of diagnosing sepsis, how does this create challenges in studying sepsis in clinical trials?

Steroids in septic shock:
Several studies have investigated the role of adjunctive corticosteroids in the management of septic shock. The largest of these studies is the ADRENAL trial, which was an ANZICS-CTG study and the largest ever trial of septic shock.
Other key trials of steroids: CORTICUS, APPROCHS and the subsequent SR-MA of the trials.

Key questions to ask re steroids:
Hydrocortisone with or without fludrocortisone?
How do the ADRENAL results compare with APPROCHS, the validity to your practice and what does the negative primary outcome result mean in the setting of potentially several secondary outcome benefits?

Magic bullets in sepsis:
- Activated Protein C – PROWESS-SHOCK (APC does not improve mortality in septic shock)
- Vitamin C – VITAMINS (JAMA 2020), ATESS (ICM 2020) and CITRIS-ALI (JAMA 2019); RCT data demonstrating no survival benefit from Vitamin C in septic shock, and potentially an increased risk of harm.

Early goal-directed therapy:
First popularised following the landmark Rivers' trial from 2001 (Rivers E et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock, ***N Engl J Med*. 2001 Nov 8;345(19):1368-77**.), in which there was a marked mortality benefit from EGDT. This led to three large international multicentre trials to assess this.
- ARISE – ANZICS-CTG study NEJM 2014
- PROCESS – NEJM 2014
- PROMISE – NEJM 2015

Review the external validity of the Rivers paper in comparison to the ARISE trial, and why the Rivers' trial may have demonstrated such a mortality benefit.

6. **Trauma**

TBI:
As well as the **Brain Trauma Foundation Guidelines,** know **DECRA (*N Engl J Med 2011*)** and **RESCUE-ICP *(NEJM 2016*)**. Thinking about the timing of intervention and the criteria for inclusion, how do the two trials of decompressive craniectomy compare and think about their validity to your practice?

Also need to include the Chestnut (NEJM 2012) study of ICP monitoring in TBI, from Bolivia/Ecuador. Think about the findings from this study and the external validity to our practice in ANZ?

The CRASH trials: Well conducted mega-trials with significant results in a truma population, but again have a serious thought about the **external** validity.
- CRASH-1 – Corticosteroids in TBI

- CRASH-2 – TXA in severe traumatic haemorrhage
- CRASH-3 – TXA in TBI

Other current topics in trauma
EPO in Trauma
Haemostatic resuscitation in trauma – types of fibrinogen

7. **Haematology / Transfusion**

Hebert, TRICC (transfusion) study, ***N Engl J Med*, 1999 Feb 11;340(6):409-17**. Patients do better if Hb kept above 70 rather than if transfused to Hb > 100. But think about the generalisability. This study was done before universal leucodepletion and includes significant biases. Comnpare this to more recent restrictive transfusion trials like in upper GI bleeding **(*NEJM 2013, 368(1):11-21*)**.
Also know the TRISS trial (NEJM 2014) investigating a restrictive vs liberal transfusion strategy in septic shock.

More modern issues include the age of blood (is 'fresher' blood better) and the use of erythropoietin. Know about the ANZ **TRANSFUSE** trial (***NEJM, 2018*)**.

Also have some understanding on the data regarding point of care haemostatic testing such as ROTEM/TEG and how they influence blood product management.

8. **Antimicrobial management**

Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. ***Chest*. 2000 Jul;118(1):146-55**. and Roberts D, Kumar A and Sharma S, Time to Appropriate Antibiotic Administration is a critical determinant in pneumonia-associated septic shock, ***Chest*, 2004, 126,724S.** I

Of interest now are the kinetics of antibiotics in ICU, particularly beta-lactams and whether continuous infusion vs intermittent dosing results in improved outcomes in severe infection. The BLING studies and the BLISS study have demonstrated some promise in earlier trials, and **BLING-III** will hopefully shed light on this and results are to be published imminently.

9. **Sedation and delirium**

This is a huge area, with studies investigating whether there is an optimum sedative in ICU, whether there is a wonder drug to prevent delirium, and whether there is a wonder drug to treat delirium. Overall, the evidence does not favour one drug over another for all-comers to ICU and this is an important point when deciding how you pick your drug for sedation and the patient population this may apply to.

Dexmedetomidine has been a key drug of focus in the recent sedation trials. The earlier studies (**PRODEX, MIDEX** - each with their methodological issues) suggested mortality benefit. The largest and most recent study is another ANZICS-CTG study - **SPICE III** (***NEJM 2019***). SPICE III showed that the use of dexmedetomidine as the primary sedative in ventilated ICU patients did not change 90 day mortality (?best primary outcome to use), but did show an increase in adverse events (bradycardia, hypotension, asystole) – particularly in the younger patients. Have a think about which patient groups might benefit from dexmed… Also, worth knowing about DahLIA (***JAMA 2016*, 315(14):1460**) which showed increased vent-free hours, quicker time to extubation, and faster resolution of delirium – though was underpowered.

In light of the potential harm to patients under the age of 65, the SPICE IV trial is currently underway looking at its use in patients >65 only.

10. **Stress ulcer prophylaxis**

    Key studies to know:
    - SUP-ICU: Pantoprazole vs placebo in patients at risk for stress ulcer development in the ICU
    - PEPTIC: PPI vs H2RA in mechanically ventilated patients

    About to be published – REVISE – large Australian ANZICS-CTG trial of PPI use in mechanically ventilated patients

11. **Liberal vs restrictive oxygen targets in ICU?**

    Hyperoxia has physiological rationale to be harmful, but the evidence is mixed for whether liberal or restrictive oxygen targets may be beneficial in reducing mortality or ventilator-free days. The most recent studies include:
    - ICU-ROX (NEJM 2019)
    - HOT-ICU (NEJM 2021)
    - LOCO-2 (NEJM 2020)

    Currently recruiting is MEGA-ROX: this is a massive multicentre RCT with three specified subgroups of interest and will hopefully give the answer as to whether there is a difference in outcomes between these two strategies.

12. **Haemodynamic monitoring and management**

    Should we be using PA catheters?
    - FACCT, ***N Engl J Med*****, 2006, 354:2213-24.** A 2x2 factorial PAC vs CVC **and** restrictive vs liberal fluid resuscitation strategy trial.
    - PACMan, ***Lancet 2005, 366:472-477***
    - A Randomized, Controlled Trial of the Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients, Canadian Critical Care Clinical Trials Group, ***N Engl J Med*** 2003;348:5-14

    More recent literature looks at the role of non-invasve assessment of filling (whether intravascularly or by ultrasound / echo) and dynamic manouevres like the Passive Leg Raise. You need to have an opinion, though the problem with all theser studies is they fail to link what is measured to any ***clinically meaningful*** endpoint.

    Management of cardiogenic shock:
    With the availability of intra-aortic balloon pumps, VA-ECMO (including ECPR) and microaxial flow pumps, have an understanding of the literature supporting each of these, the situations in which they may be used, and most importantly how it pertains to your practice and the centre in which you work!

Good luck,
Ian Seppelt
Nov 5th, 2018

2024 update by Dr Karthik Venkatesh and Dr Joshua Pillemer

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page..
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.