DOCTOR OF PHILOSOPHY

PRECIS-2

Making trials matter: providing an empirical basis for the selection of pragmatic design choices in clinical trials

Loudon, Kirstine

Award date:
2015

Awarding institution:
University of Dundee

Appendix

Chapter 4 Delphi Process

Dear ,

I am doing a PhD entitled "*Making trials matter: providing an empirical basis for the promotion (or rejection) of pragmatic design choices in clinical trials*". You cited the Thorpe KE, Zwarenstein M, Oxman AD, et al. paper entitled "A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers." in your paper "*Name, Title, Reference*" and I wondered whether you would be interested in helping us with this research.

We have received funding from the Chief Scientist Office in Scotland to undertake further work on PRECIS, and I am writing to ask for your help with the first phase of the project.
The first phase starts in October and would involve answering a *Survey Monkey* questionnaire on PRECIS that would take about 10 minutes to complete. If you complete the survey and let us know your name we will acknowledge your input in future publications. https://www.surveymonkey.com/s/PRagmaticExplanatoryContinuumIndicatorSummaries.

If you are interested in participating in a further round of Survey monkey we would be grateful for your help. In addition, you may also be interested in assisting with further phases of the project to validate to PRECIS, all data will be anonymised. The second phase (December to April 2013) is one to one or group testing of different PRECIS models using a topic guide. This would entail participants answering questions on the PRECIS domains (looking at different aspect of trial design), scoring and structure of the proposed PRECIS models. This could take up to 1 hour at sessions in London Ontario in Canada or at the University of Dundee in Scotland. We would like to audio record the sessions, to assist in analysis, unless participants do not give consent. There is limited funding available for UK participants to attend meetings in Dundee.

Finally, the third phase, would involve using the modified PRECIS model, PRECIS 2, to score a sample of 15 trials over a two month period by e-mail. We can provide some funding for raters involved in Phase 3 work. All participation is strictly voluntary and you can leave at any stage in the project. If

you are interested in participating in any of the phases do get in touch or let me know when completing this section in the Survey Monkey questionnaire. Feel free to pass on this e-mail to anybody you think might be interested in participating in the project.

If you require further information please do not hesitate to get in touch. My e-mail address is: k.loudon@dundee.ac.uk

We hope you will consider helping us with this important research on clinical trial design and look forward to hearing from you at your earliest convenience.

Kirsty Loudon (PhD Student), University of Dundee

On behalf of Shaun Treweek, Frank Sullivan, Merrick Zwarenstein, Peter Donnan

(PhD Supervisors and co-applicants on CSO grant CZH/4/773 **MAKING CLINICAL TRIALS MORE RELEVANT: IMPROVING AND VALIDATING THE PRECIS TOOL FOR MATCHING TRIAL DESIGN DECISIONS TO TRIAL PURPOSE**)

CHIEF SCIENTIST OFFICE

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Box 4.1 Example Invitation e-mail with title: PRECIS – PRagmatic Explanatory Continuum Indicator Summaries

Chapter 5 Brainstorming – first meeting

Subject: PRECIS brainstorming session (PRagmatic Explanatory Continuum Indicator Summary) trial design tool

Hi,

I started a PhD in October, supervised by Shaun Treweek, Frank Sullivan and Merrick Zwarenstein, looking at pragmatic trials, in particular validating a tool to help trialists design pragmatic trials, called PRECIS. I believe PRECIS could be very useful for designing real world trials that are useful to clinicians and policymakers.

I am writing to invite you to join a brainstorming meeting to discuss trial design and the PRECIS tool. Participants would be from Dundee University and we would meet at the Mackenzie Building. The group would run from 1pm to 3pm, with lunch available from 12.30. Our provisional date for the meeting is Friday 8th June although we can change this. I have attached a training package for PRECIS to give you some information about the tool and how it was used with two example trials. I have also attached the original article describing PRECIS which gives further information: Thorpe et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. Journal of Clinical Epidemiology 2009; 62: 464-475.

If you can attend please let me know and I will then send two short trials that I would like to discuss at the meeting so that I can get some input into developing the tool.

I would be very grateful for any time and help you can give to this project and look forward to hearing whether or not you will be able to attend.

Best wishes

Kirsty

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Email: K.Loudon@dundee.ac.uk
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Mob: 0779 694 7551

Box 5.1 Invitation to attend first brainstorming meeting in Dundee with local participants

Agenda **Friday 8th June 1-3pm 2012**

1. Introductions:
    a. KL and ST
    b. Audio transcript – introductions for everyone in the room (first, last name and department)
2. What did group think about PRECIS? First impressions using PRECIS
3. Brief discussion about tool, why are we doing this – improve PRECIS - KL
4. Jolly example – ST - discuss
5. Price example – KL- discuss
6. Questions (topic guide of questions but include: domains missed out, not necessary, scoring, weighting, strengths/weaknesses, difficulty in scoring, anything else)
7. Close

Box 5.2 Agenda for first brainstorming meeting, Dundee 8th June 2012.

From: Kirstine Loudon
Sent: 12th November 2012 10.51
To:
Subject: PRECIS - PRagmatic Explanatory Continuum Indicator Summaries

Dear X,

I am doing a PhD entitled "*Making trials matter: providing an empirical basis for the promotion (or rejection) of pragmatic design choices in clinical trials*" and I wondered whether you would be interested in helping us with this research by attending a meeting in March 2013 in London, Ontario or Toronto.

We would like to discuss results from a modified Delphi carried out in October and November 2012 and proposed modifications of the original PRECIS model. This would entail participants discussing the PRECIS domains (looking at different aspect of trial design), scoring and structure of possible PRECIS models. This could take up to 2 hours at sessions in London Ontario in Canada or Toronto in Canada. Funding is limited, so if you would like to attend you would need to use your own travel and accommodation budget. We are currently uncertain if we can fund full videoconferencing for the meetings. If you can attend, please let me know which destination suits you best: London, Ontario or Toronto? I have set up a Doodle poll with possible dates in March so would be grateful if you would click on this link and or feel free to respond to this e-mail http://www.doodle.com/4g5fcgk9vpt5eh29 by Monday 19th November.

If you require further information please do not hesitate to get in touch. My e-mail address is: k.loudon@dundee.ac.uk

We hope you will consider helping us with this important research on clinical trial design and look forward to hearing from you at your earliest convenience.

Best wishes

Kirsty Loudon (PhD Student), University of Dundee

On behalf of Shaun Treweek, Merrick Zwarenstein, Frank Sullivan, Peter Donnan
(PhD Supervisors and co-applicants on CSO grant CZH/4/773 **MAKING CLINICAL TRIALS MORE RELEVANT: IMPROVING AND VALIDATING THE PRECIS TOOL FOR MATCHING TRIAL DESIGN DECISIONS TO TRIAL PURPOSE**)

Kirsty Loudon

PhD student, University of Dundee

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Brainstorming – second meeting

Box 5.3 Invitation to attend second brainstorming meeting in Toronto who had not been involved in the modified Delphi

From: Kirstine Loudon
Sent: Fri 11/01/2013 12:11
To: 'Daniel L Riddle' <dlriddle@vcu.edu>; 'Moher, David' <dmoher@ohri.ca>; 'Krishnan, Jerry' <jakris@uic.edu>; louis.fiore@va.gov; vivian.welch@uottawa.ca; Joel Gagnier PhD (jgagnier@med.umich.edu); kevin.thorpe@utoronto.ca; anwen.chan@utoronto.ca; rob.fowler@sunnybrook.ca; malcolm.maclure@ubc.ca; 'Kent, David' dkent1@tuftsmedicalcenter.org
CC: 'gallardo@uic.edu'; murray.krahn@theta.utoronto.ca; merrick.zwarenstein@ices.on.ca; 'Lutz, Jennifer S' <Jlutz@tuftsmedicalcenter.org>; Shaun Treweek <streweek@mac.com>
Subject: Pragmatic Trials - PRECIS meeting Monday 11th March 9.30-5pm Toronto, Canada

Happy New Year!

We are going ahead with **Monday 11th March 9.30-5pm**. I am delighted that the meeting is being hosted by Murray Krahn, Professor, Department of Medicine and Faculty of Pharmacy, University of Toronto Director and being held *at THETA, F. 144 College Street, Rm 600, Toronto ON, M5S 3M2.*

Could you please confirm you are still able to attend, there will probably be 14 of us: Dan Riddle, David Moher, Jerry Krishnan, Lou Fiore, Vivian Welch, Joel Gagnier, Kevin Thorpe, An When Chan, possibly Rob Fowler, David Kent, and Malcolm Maclure, as well as Merrick Zwarenstein, my PhD supervisor who is helping facilitate the meeting, our host Murray Krahn and me.

We are uncertain at present if we will have web conferencing.

DRAFT PRECIS Meeting Agenda

1. Present Chief Scientist Office (CSO) grant project on PRECIS – Pragmatic Explanatory Continuum Indicator Summaries - 4 phases
2. Results from Phase 1 on PRECIS project, modified DELPHI 2 rounds carried out in October and November 2012
3. Phase 2 - Presentation of Modified PRECIS models prepared based on Round 1 results
4. Discussion on models – audiotaped if ok with everyone at meeting.
   Participants discuss the PRECIS domains (looking at different aspect of trial design), scoring and structure of possible PRECIS models.

Break for lunch

Afternoon discussion

- new approach to significance testing for pragmatic trials

or

- plan a PRECIS elaboration paper, a detailed paper that picks out each of the assertions or ideas for PRECIS and gathers the evidence.

I look forward to hearing if you can join us. Funding is limited, so if you would like to attend you would need to use your own travel and accommodation budget but THETA is kindly providing refreshments and lunch will be provided. CSO will also pay for taxis to and from the airport.

For those out of town, suggestions for accommodation close to THETA are:

- Madison Manor Boutique Hotel - Toronto, Ontario Canada http://madisonmanorboutiquehotel.com/ which has a good reputation, just a few yards north of Bloor street. Also about 15 minutes walk and one subway stop away the meeting venue.
- The Holiday Inn http://www.holidayinn.com/hotels/us/en/toronto/yyzct/hoteldetail/directions, on Bloor

street between st georges street and spadine avenue- also one subway stop or about 15 minutes walk from the meeting venue

- Primrose Hotel http://www.torontoprimrosehotel.com/contact/directions

Any questions do get in touch. Maps are attached.

Best wishes

Kirsty

Kirsty Loudon

PhD student, University of Dundee

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Box 5.4 Confirmation Invitation with Agenda for second brainstorming meeting in Toronto

From: Joanna Bielecki <joanna.bielecki@theta.utoronto.ca>
Sent: 5th March 2013 15.13
To: Eric.S.Johnson@kpchr.org; powersjohn@mail.nih.gov; Peter_Selby@camh.net; Noemilois@aol.com; jsegal@jhsph.edu; Janet.Martin@lhsc.on.ca; Kirstine Loudon <k.loudon@dundee.ac.uk>
Subject: TRIAL: for video-conferencing PRECIS Meeting in Toronto

Hello Everyone,

I am one of the organizers of PRECIS Meeting in Toronto, and in charge of the technical support for video-conferencing portion of the meeting. I would like to invite you to a **trial** video-conference meeting on Thursday, March 7th, 2013. I will be sending official invitations to this trial meeting tomorrow, with full instructions on how to connect and test your system. The trial will run as a continuous meeting, you would be able to connect to the trial at any time between 10am - 5pm EST. This will be an opportunity for you to **test** your local systems **configuration and connectivity** before the March 11th PRECIS conference in Toronto; so that if any problems arise you will have a chance to consult your local IT support and correct the problems. I hope this will be helpful to avoid any technical delays on the day of the PRECIS conference.

Best wishes and hope to hear from you on March 7th.

Joanna Bielecki
Research Librarian

Toronto Health Economics and Technology Assessment Collaborative (THETA)
Leslie Dan Pharmacy, University of Toronto
144 College Street, 6th Floor Room 679
Toronto, ON M5S 3M2
joanna.bielecki@theta.utoronto.ca
416-946-0583
theta.utoronto.ca

Box 5.5 Invitation to attend video conferencing at second brainstorming meeting in Toronto

Third Brainstorming meeting

From: Kirstine Loudon
Sent: 12 April 2013 12:04
To: Peter Donnan; Shaun Treweek; Roberta Littleford; Thomas Lamont; Frank Sullivan, Fiona Hogwarth
Subject: PhD assistance with domains for PRECIS-2 - tool to improve the applicability of RCTs

Hi,
I would like to have further input to improving the PRECIS tool following the Delphi results and a meeting in Toronto with a group of methodologists, statisticians, policy makers and doctors.

Back in June last year I appreciated input from you Peter, Thomas, Fiona and unfortunately you were unable to attend Roberta. I wondered if you would be available for an hour Monday 22nd April at for instance 1pm with Frank and Shaun my PhD supervisors to meet at the Mackenzie building? So checking availability for you all, if not then would later in the day be better 2.30/3pm after a meeting on the Tonsillectomy trial you are having with Roberta, Frank?

I look forward to hearing from you and if not would Tuesday 23rd or Monday 29th April be better?

Best wishes

Kirsty

Kirsty Loudon

PhD student, University of Dundee

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Box 5.6 Reminder to attend third brainstorming meeting in Dundee

From: Kirstine Loudon
Sent: 26 April 2013 17:05
To: Roberta Littleford; Shaun Treweek; Frank Sullivan; Peter Donnan; Thomas Lamont
Subject: Reminder: PhD assistance with domains for PRECIS-2 - tool to improve the applicability of RCTs

Hi,
Apologies for the late reminder. Just to confirm I look forward to seeing you on Monday 29th April 12.30-2pm at the Mackenzie building, we are downstairs in CTA. As it is over lunch, I have ordered some sandwiches and coffee.

Greatly appreciate your help and I look forward to seeing you for any or all of the time we have the meeting room booked.

Have a good weekend.

Best wishes

Kirsty

Kirsty Loudon

PhD student, University of Dundee

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Box 5.7 Reminder to attend third brainstorming meeting in Dundee

Post Brainstorming prior to user testing

*We recommend that trialists or others assessing whether design decisions are **fit for purpose**, do this iteratively using six steps:*

1. Describe the purpose of the trial: [choosing between options, revealing expected benefits.

2. Specify the settings and participants to which the findings of the trial are applicable, and the organizational changes, resources and training to be added to conduct the trial.

3. Specify the design options at the pragmatic and explanatory extremes of each domain

4. Consider your trial design choices for each domain.

5. Score these choices according to how pragmatic or explanatory each is in relation to the extremes for each domain and make a mark between pragmatic and explanatory on the wheel spoke for 'score 1-5' or 'score 1-7'.

6. Review design choices (5) against purpose (1) and decide whether your trial design decisions match your intended purpose. Modify and re-iterate if required.

NB: To avoid confusion in terminology, we have carefully split the participants involved in clinical trials into intervention-care recipients and intervention-care delivery participants.

Box 5.8 PRECIS 2 training instructions for PRECIS-2

1.To improve trial Generalisability of Results

Now have at beginning of each domain:
"The similarity between…DOMAIN…

And at the end of each domain:
in the setting to which the results will be applied."

Box 5.9 Key PRECIS-2 difference

•Recruitment path

•Setting

•Similarity between the resources, provider expertise and the organisation of care delivery, in the **intervention** arm of the trial.

•Similarity between the resources, provider expertise and the organisation of care delivery, in the **comparison** arm of the trial

Box 5.10 PRECIS-2 DOMAIN differences

CONSENT FORM - Participant's copy

Title of Project: MAKING CLINICAL TRIALS MORE RELEVANT: IMPROVING AND VALIDATING THE PRECIS TOOL FOR MATCHING TRIAL DESIGN DECISIONS TO TRIAL PURPOSE

Name of Researcher: Kirsty Loudon

		Put a tick in
1	I confirm that I have understood the information given to me for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason	
3	I give my permission for the discussion to be audio recorded.	
4	I understand that the notes and transcripts of the discussion may be looked at by individuals from the University of Dundee (the Sponsor of the	
5	I agree to take part in the above study.	

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Box 6.2 Participant Consent form

Chapter 7 – Validity and Reliability study

Dear ,
As you may recall, I am doing a PhD entitled "*Making trials matter: providing an empirical basis for the promotion (or rejection) of pragmatic design choices in clinical trials.* Previously you indicated you would be interested in helping us with the third phase of this research funded by the Chief Scientist Office in Scotland.

We are building on the work to develop the PRECIS (PRagmatic Explanatory Continuum Indicator Summaries) tool to design clinical trials that are more relevant. The protocol was published in April (Making clinical trials more relevant: improving and validating the PRECIS tool for matching trial design decisions to trial purpose Trials, 14:115.)

We would like you to use the modified PRECIS model, PRECIS-2, to score a sample of 15 trial protocols over a two month period. PRECIS-2 has been developed using a Delphi survey, brainstorming through meetings in Toronto and Dundee and user testing with an international group of trialists and researchers.

Can you please confirm that you are still interested in assisting? We can provide payment if you help us with this Phase 3 work of approximately $160 (£100) depending on how many people agree to take part. As soon as you confirm your interest, I will send out a batch of five trial protocols every two weeks, with a 3 page PRECIS-2 user guide and a PRECIS-2 wheel and table for you to use to score each protocol.

If you require further information please do not hesitate to get in touch. My e-mail address is: k.loudon@dundee.ac.uk

We really hope you will help us with this important research on clinical trial design and look forward to hearing from you at your earliest convenience.

Kirsty Loudon (PhD Student), University of Dundee
On behalf of Shaun Treweek, Frank Sullivan, Merrick Zwarenstein, Peter Donnan
(PhD Supervisors and co-applicants on CSO grant CZH/4/773 **MAKING CLINICAL TRIALS MORE RELEVANT: IMPROVING AND VALIDATING THE PRECIS TOOL FOR MATCHING TRIAL DESIGN DECISIONS TO TRIAL PURPOSE**)

CHIEF SCIENTIST OFFICE

Box 7.1 Example invitation e-mail with title: Invitation to participate in the validity and reliability testing of PRECIS-2

Hi,
Just sending a quick reminder to encourage you to help validate PRECIS-2.

As I believe Shaun mentioned, this would involve using the modified PRECIS model, PRECIS-2, to score a sample of 15 trials over a 6 week period, so by 1st November. I am hoping you can do all 15 but it would be a great help if you could do 5 or 10 depending on time. So far testers are returning saying taking "less than the 20mins per protocol" so hope that you can get back to me soon.

Please score the protocols using the PRECIS-2 wheel or using the table with a 1-5 Likert score (5 being very pragmatic, 1 very explanatory). If using the wheel, feel free to write notes on the paper, take a copy, and send to me in Dundee or scan in and e-mail me - Kirsty. If scoring using the table, and think there is some uncertainty, please jot down rationale.

I look forward to hearing from you, with your scores for the 5 protocols. I will then send you another batch of 5 protocols if you can continue to help with this work. Don't hesitate to get in touch if you have any questions.

Thank you for your interest in the project.
Best wishes

Kirsty

Box 7.2 Example of deadline reminder e-mail with title: PRECIS-2 validation work 5 protocols

Chapter 7C Validity and reliability raw results with sensitivity analysis

ELIGIBILITY

Results 1

Sample: 5 trial protocols, 18 raters

4 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, 3 not done due to time and 1 due to lack of expertise in the area (physiotherapist). Imputed values 4/90 = 4.4% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.455[a]	.196	.881	16.041	4	68	.000
Average Measures	.938	.814	.993	16.041	4	68	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

10 trials, 12 raters

2 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, both not done due to lack of expertise in the area (physiotherapist) – one rater missed out whole trial as not area of expertise (not just domain). Imputed values 2/120 = 1.67% of data.

Intraclass Correlation Coefficient							
	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.405[a]	.205	.716	9.177	9	99	.000
Average Measures	.891	.755	.968	9.177	9	99	.000

Results 3

Sample 15 trials, 7 raters

1 imputed value at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, 1 not done due to lack of expertise in the area (physiotherapist). Imputed values 1/135 = 0.74% of data.

Intraclass Correlation Coefficient							
	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.506[a]	.302	.741	8.157	14	84	.000
Average Measures	.877	.752	.952	8.157	14	84	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data Eligibility criteria

Rater Info.	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
4 physiotherapist	4	"No entry, obviously no content knowledge on this one. Too far afield of my content to judge."
6	Did not do 11, 12, 13, 14, 15 due to time	
8	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11. Kinesology, systematic reviewer	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12	Did not do 11, 12, 13, 14, 15 due to time. 7 as no expertise in area	
13	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
14	Did not do 11, 12, 13, 14, 15 due to time	
15	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

RECRUITMENT

Results 1

Sample: 5 trial protocols, 18 raters

4 imputed values at 3 = equally pragmatic/explanatory. 1 due to "inadequate information" and 3 due to "lack of time". Thus complete set for ICC analysis, 3 not done due to time and 1 due to lack of expertise in the area (physiotherapist). Imputed values 4/90 = 4.4% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.214[a]	.052	.729	5.912	4	68	.000
Average Measures	.831	.496	.980	5.912	4	68	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2.

Sample 10 trials, 12 raters

2 imputed value at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, 2 not done due to lack of expertise in the area (physiotherapist, medical doctor). Imputed values 2/120 = 1.67% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.112[a]	.010	.386	2.509	9	99	.012
Average Measures	.601	.105	.883	2.509	9	99	.012

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 3

Sample 15 trials, 7 raters

1 imputed value at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, 1 not done due to "lack of information"). Imputed values 1/135 = 0.74% of data.

First analysis

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.159[a]	.020	.416	2.321	14	84	.009
Average Measures	.569	.127	.833	2.321	14	84	.009

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Note for discussion:

Rater 3 (Bridget Gaglio) results very different to everyone else: 1 compared to 5 for several trials (10, 11, 14, 15). Co-author with Russ Glasgow (trialists complex interventions) worked on trials using PRECIS-1, did 15 protocols within 2 weeks, experienced rater. When looked at rationale for rating – no information. She also stated when queried when results first submitted "if the information was not provided I scored it a one instead of guessing base on the other information in the protocol. Thus PRECIS-2 score changed to "3" = equally pragmatic/explanatory so consistency across raters for issue of "lack of information".

Rater 7 (Marion Campbell), experienced trialists, also consistently higher than others – stated "standard recruitment path".

2nd analysis

Sample 15 trials, 7 raters

5 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, 5 due to lack of information in protocol. Imputed values 5/105 = 4.76% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.173[a]	.030	.433	2.460	14	84	.006
Average Measures	.594	.176	.842	2.460	14	84	.006

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data Recruitment

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
3	10	"No mention of how patients will be recruited"
3	11	"no information on how participants were recruited at the various sites"
3	14	"no information on how patients will be recruited only states type of patients included: informed consent will be obtained"
3	15	"Unclear how patients are recruited for the study"
4. physiotherapist	10	"content knowledge extremely critical to judge this one…)"
5.	3, 9, 13	Unclear so gave "3" score
6.	Did not do 11, 12, 13, 14, 15 due to time	
7	1, 2, 4, 5, 7, 9, 10, 11, 13, 14, 15	"Standard recruitment path"
8	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11. Kinesology, systematic reviewer	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12.	Did not do 11, 12, 13, 14, 15 due to time. 7 as no expertise in area	
13.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
14	Did not do 11, 12, 13, 14, 15 due to time	
15. medical practitioner, trialist	2	"inadequate information"
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	

Rater	Protocol	Rationale quote from rater
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

SETTING

Results 1

Sample: 5 trial protocols, 18 raters

4 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, 3 not done due to time, 1 "unclear to judge". Imputed values 4/90 = 4.4% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.386[a]	.149	.850	12.339	4	68	.000
Average Measures	.919	.758	.990	12.339	4	68	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

Sample 10 trials, 12 raters

2 imputed value at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis, 1 not done due to insufficient information to judge, one entire protocol (not just domain) due to medical practitioners's lack of knowledge in the trial area. Imputed values 2/120 = 1.67% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.254[a]	.095	.576	5.086	9	99	.000
Average Measures	.803	.559	.942	5.086	9	99	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 3

Sample 15 trials, 7 raters

1 imputed values at 3 = equally pragmatic/explanatory, not done as "unclear to judge". Thus complete set for ICC analysis. Imputed value 1/105 = 0.95% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.371[a]	.179	.636	5.128	14	84	.000
Average Measures	.805	.605	.924	5.128	14	84	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data for Setting

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
3.	4	"It is unclear to me which are the recruitment and intervention centres, so I cannot say if there are referral special centres or not"
4, clinician, trialists	4	"was u unclear to me what setting"
6.	Did not do 11, 12, 13, 14, 15 due to time	
8	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11. Kinesology, systematic reviewer	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12.	Did not do 10, 11, 12, 13, 14, 15 due to time. 7 as no expertise in area	
13.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
14	Did not do 11, 12, 13, 14, 15 due to time	
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

Organisation

Results 1

Sample: 5 trial protocols, 18 raters

There were six imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis. Three scores not done due to lack of time, one due to lack of expertise in the area (physiotherapist) and one as inadequate information, and 2 due to difficulty scoring . Imputed values 6/90 = 5.55% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.142[a]	.018	.641	3.971	4	68	.006
Average Measures	.748	.249	.970	3.971	4	68	.006

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

10 trials, 12 raters

Imputed values at 3 = equally pragmatic/explanatory for 2 scores – 2 not done due to lack of expertise in the area (physiotherapist). One entire protocol (not just domain)was missed out due to medical practitioners' lack of knowledge in the trial area and same rater thought "The new organisation domain is very complex" so missed out scoring 6 trials for the "Organisation" domain. Thus complete set for ICC analysis. Imputed values 9/120 = 7.5% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.286[a]	.117	.610	5.807	9	99	.000
Average Measures	.828	.613	.949	5.807	9	99	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 3

Sample 15 trials, 7 raters

2 imputed values at 3 = equally pragmatic/explanatory thus complete set for ICC analysis. Imputed values 2/105 = 1.90% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.270[a]	.099	.541	3.584	14	84	.000
Average Measures	.721	.435	.892	3.584	14	84	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data Organisation

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
4. Physiotherapist	Did not complete this domain in 4, 10	"Too far afield of my content to judge. Don't know enough"
5. Trialist	Did not complete this domain in 15	"Unclear whether it is clearly different from routine care at those centers."
6.	Did not do 11, 12, 13, 14, 15 due to time	
8.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11.	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12. medical practitioner, trialist	Did not complete this domain in 4, 5, 6, 8, 9, 10	"The new organisation domain is very complex"
12. medical practitioner, trialist	Did not do 11, 12, 13, 14, 15 due to time. 7 as no expertise in area	
13.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
14	Did not do 11, 12, 13, 14, 15 due to time	
15. medical practitioner, trialist	Did not complete this domain in 4	"was unclear to me what level of organization was to be used"
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

Flexibility of experimental intervention – Delivery

Results 1

Sample: 5 trial protocols, 18 raters

There were six imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis. Three scores not done by same rater due to due to lack of expertise in the area (physiotherapist), three protocols due to time (2 raters). Imputed values 6/90 = 6.67% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.375[a]	.141	.844	11.804	4	68	.000
Average Measures	.915	.747	.990	11.804	4	68	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

Sample: 10 trials, 12 raters

There were 6 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis. Three scores not done by same rater due to due to lack of expertise in the area (physiotherapist), three protocols due to time (2 raters). Imputed values 6/90 = 6.67% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.325[a]	.144	.648	6.787	9	99	.000
Average Measures	.853	.669	.957	6.787	9	99	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 3

Sample 15 trials, 7 raters

There were 3 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis. Three scores not done by same rater due to due to lack of expertise in the area (physiotherapist). Imputed values 3/90 = 3.33% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.289[a]	.113	.560	3.839	14	84	.000
Average Measures	.740	.472	.899	3.839	14	84	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data Flexibility of experimental intervention – Delivery

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
4. Physiotherapist	4, 5, 10	"Too far afield of my content to judge. Don't know enough"; "Just too difficult for me to judge given lack of understanding of usual care expectations"
5.	5	"Standardised and inflexible CS procedures"
6.	Did not do 11, 12, 13, 14, 15 due to time	
8.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12 medical practitioner, trialist		It is still a problem if the trial compares two or more interventions (see my rating on Azuara-Blanco), which are different in flexibility, this needs guidance, furthermore information is needed how to handle adjunct treatment to usual care versus usual care only, is usual care only no intervention or also rated as intervention which would be always end up with 5 and might be totally different than the intervention, making it difficult to decide on a number between 1 and 5.
12 medical practitioner, trialist	Did not do 11, 12, 13, 14, 15 due to time	
12 medical practitioner, trialist	Did not do 7	"as not area of expertise"
13.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15	

Rater	Protocol	Rationale quote from rater
	due to time	
14	Did not do 11, 12, 13, 14, 15 due to time	
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

Flexibility of experimental intervention - Adherence

Results 1

Sample: 5 trial protocols, 18 raters

There were EIGHTEEN imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (see reasons below) mainly due to lack of information in protocol. Imputed values 14/90 = 15.56% of data

Intraclass Correlation Coefficient

	Intraclass	95% Confidence Interval	F Test with True Value 0

	Correlation[b]	Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.124[a]	.010	.613	3.542	4	68	.011
Average Measures	.718	.159	.966	3.542	4	68	.011

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

Sample: 10 trials, 12 raters

There were 4 + 4 + 4 + 2 +3 = 17 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (see reasons below) mainly due to lack of information in protocol. Imputed values 17/108 = 15.74% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.101[a]	.004	.368	2.343	9	99	.019
Average Measures	.573	.042	.875	2.343	9	99	.019

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 3

Sample 15 trials, 7 raters

There were eight imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis. Problems with rating arose due to one rater stating there was a lack of information in protocol and had no knowledge of the clinical area (3, 4, 5, 10, 13 protocol) and another rater stating lack of information (3 protocols 1, 8, 9). Imputed values 8/105 = 7.62% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.043[a]	-.053	.254	1.312	14	84	.218
Average Measures	.238	-.544	.705	1.312	14	84	.218

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 4 NO missing data

5 raters, 15 trials

Intraclass Correlation Coefficient							
	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.166[a]	-.011	.459	1.997	14	56	.035
Average Measures	.499	-.056	.809	1.997	14	56	.035

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data Flexibility of experimental intervention - Adherence

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
3. Trialist	1, 8,9	"Not mentioned"
4. Physiotherapist	3	Not addressed in protocol
4. Physiotherapist	3, 4, 5, 10, 13	Too far afield of my content to judge. Don't know enough,
5. Trialist	3, 4, 5	"no patient removed due to lack of adherence"; "no evidence of selective exclusion"; "deviations allowed but recorded";
6. Physiotherapist	4, 5, 7, 10	"unclear, no information about usual adherence and encouragement to adhere in the trial"; "I don't think this is an item in this trial".
6.	Did not do 11, 12, 13, 14, 15 due to time	
8.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11	Did not do 2, 6, 7, 8, 9, 10,	

Rater	Protocol	Rationale quote from rater
	11, 12, 13, 14, 15 due to time	
12.	1, 3, 6 domains not scored	"although mentioned in most study protocols in protocol publications often not enough information is given to judge on this"
12. medical practitioner, trialist	Did not do 11, 12, 13, 14, 15 due to time, 7 as no expertise in area	
13.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
14. Nurse, trial methodologist	1, 5, 9	"Not clear", "Not reported", "not clear if have to attend all sessions – some information on withdrawals".
14.	Did not do 11, 12, 13, 14, 15 due to time	
15. medical practitioner, trialist	2, 4, 5	"not discussed"; "unclear to me; intervention is directed at physician who is to follow "local protocol", however, there is no explicit statement that adherence will not be promoted beyond usual care"; "inadequately described or not reported – I could not find it";
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16.	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19. medical practitioner, trialist	3, 4, 5	"not described"; "N/A one time surgery"; N/A one time infusion".
19.	Did not do 11, 12, 13, 14, 15 due to time	

Follow up

Results 1

Sample: 5 trial protocols, 18 raters

There were 6 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (4 protocols not completed due to time, 2 as not reported in protocol). Imputed values 6/90 = 6.67% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.240[a]	.064	.753	6.677	4	68	.000
Average Measures	.850	.554	.982	6.677	4	68	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

Sample: 12 trial protocols 10 raters

There were 8 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (3 protocol not completed due to time, 5 as not reported in protocol or uncertain). Imputed values 8/90 = 8.89% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.252[a]	.094	.574	5.035	9	99	.000
Average Measures	.801	.554	.942	5.035	9	99	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Result 3

Sample: 15 trial protocols and 7 raters

There was one imputed value at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis). Imputed values 1/90 = 1.11% of data

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.174[a]	.031	.435	2.479	14	84	.005
Average Measures	.597	.183	.844	2.479	14	84	.005

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data Follow up

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
3.	8	"not mentioned"
6.	9	?
6.	Did not do 11, 12, 13, 14, 15 due to time	
8.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11.	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12. medical practitioner, trialist	Did not complete this domain in 1, 3	

Rater	Protocol	Rationale quote from rater
12. medical practitioner, trialist	Did not do 11, 12, 13, 14, 15 due to time. 7 as no expertise in area	
13.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
14	4	"Not reported"
14	Did not do 11, 12, 13, 14, 15 due to time	
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

Outcome

Results 1

Sample: 5 trial protocols, 18 raters

There were 3 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (3 protocols not completed due to time). Imputed values 3/90 = 3.33% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.231[a]	.060	.745	6.404	4	68	.000
Average Measures	.844	.535	.981	6.404	4	68	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

Sample: 12 trial protocols 10 raters

There was 1 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (1 protocols not completed due to time). Imputed values 1/90 = 1.11% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.139[a]	.025	.429	2.938	9	99	.004
Average Measures	.660	.236	.900	2.938	9	99	.004

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Result 3

Sample: 15 trial protocols and 7 raters

Complete set for ICC analysis, no imputed values.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.101[a]	-.017	.340	1.788	14	84	.054
Average Measures	.441	-.134	.783	1.788	14	84	.054

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Notes for discussion

Odd results 2 and 5 scores for protocol 12; "2" by rater 7 "very tight outcome seriologically confirmed" and "2" for rater 4 for protocol 12 "daily diary far removed from usual care"

Missing data Outcome

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
6.	Did not do 11, 12, 13, 14, 15 due to time	
8.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
11	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12. medical practitioner, trialist	Did not do 11, 12, 13, 14, 15 due to time. 7 as no expertise in area	
13.	Did not do 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	

Rater	Protocol	Rationale quote from rater
14	Did not do 11, 12, 13, 14, 15 due to time	
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	Did not do 11, 12, 13, 14, 15 due to time	
17.	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

Analysis

Results 1

Sample: 5 trial protocols, 18 raters

There were 5 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (3 protocols not completed due to time + 2 due to lack of information). Imputed values 5/90 = 5.55% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig

Single Measures	.214[a]	.052	.729	5.905	4	68	.000
Average Measures	.831	.495	.980	5.905	4	68	.000

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Results 2

Sample: 12 trial protocols 10 raters

There were 3 imputed values at 3 = equally pragmatic/explanatory. Thus complete set for ICC analysis (1 protocols not completed due to time and 3 values not in protocol). Imputed values 3/90 = 3.33% of data.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.182[a]	.050	.489	3.667	9	99	.001
Average Measures	.727	.388	.920	3.667	9	99	.001

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Result 3

Sample: 15 trial protocols and 7 raters

Complete set for ICC analysis, no imputed values.

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.221[a]	.064	.489	2.990	14	84	.001
Average Measures	.666	.322	.870	2.990	14	84	.001

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Missing data Analysis

Rater	Protocol	Rationale quote from rater
2.	Did not do 11, 12, 13, 14, 15 due to time	
4	8	"No mention of ITT, per protocol discussed at length"
6	1, 8 , 10	"Not clear, the sentence "data cleaning…." Suggests it to be more explanatory";
11	Did not do 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
12	Did not complete this domain in 3, 5	"not clear if ITT or PP primary analyses".
12	Did not do 11, 12, 13, 14, 15 due to time. 7 as no expertise in area	
13	4	- (none given)
13.	Did not do 6, 7, 8, 9, 10, 11, 12,	

Rater	Protocol	Rationale quote from rater
	13, 14, 15 due to time	
14	Did not do 11, 12, 13, 14, 15 due to time	
15.	Did not do 7, 8, 9, 10, 11, 12, 13, 14, 15 due to time	
16	2	"Analysis is not ITT as excludes all participants who do not take first dose."
16	Did not do 11, 12, 13, 14, 15 due to time	
17	Did not do 2, 4, 9, 10, 11, 12, 13, 14, 15 due to time	
18.	Did not do 1, 2, 3, 4, 11, 12, 13, 14, 15 due to time.	
19.	Did not do 11, 12, 13, 14, 15 due to time	

Chapter 8 Internal and external validity

Table 8.1 with details of variables in proposed matched studies

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
Bots 2005[23]	Rosuvastatin 10mg	Achieving European LDL-C goal (<3.0 mmol/l) at week 12	152 primary care centres in Netherlands	1215	4 (rather pragmatic)	61 (9.7) for intervention; 62 (9.2), 62 (9.3), and 60 (9.3) for comparator	CHD risk at baseline. Very high (>40%): 34% intervention; 34, 38, 27% for comparators	12 weeks	**RD 17.16%** More patients achieved 1998 and 2003 European goals w. Rosuvastatin ($p < 0.001$); 75.4% Rosusvastatin 10mg achieved vs Arovastatin 10mg 58.7%	Unclear
Davidson [24]	Rosuvastatin 10mg	% change in LDL cholesterol from baseline - week 12 (European	52 in North America	519	2 (rather explanatory)	56.4-57.9 ± 12.7	Fasting low density lipoprotein (LDL) cholesterol ≥ 4.8 mmol/L (0.5) all	12 weeks	**RD 11.15%** Secondary outcome to match outcome in Bots trial:84% Rosuvastatin	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
		goal at week 12 was 2ndry goal					groups		10mg achieved vs 73% Arovast-atin 10mg	
Brady [15]	B-blocker – metoprolol	Fatal and non-fatal cardiovascular events (namely MI, unstable angina, ventricular tachycardia, or stroke) within 30 days of operation	4	103	3 (= explanatory/ pragmatic)	Placebo74 median (66-76); Metoprolol 73 (61-79)	Requiring vascular surgery	32 months: From July 2001 and March 2004	RD = -0.34% NS	-
Yang[25]	B-blocker metoprolol	Fatal and non-fatal cardiovascular events (namely MI, unstable	3	496	2(rather explanatory)	Placebo 65.9±10; Metropol	Requiring vascular surgery	3 years 36 months	RD – 1.84% RRD 15.3% (95%CI -38.3%	-

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
		angina, ventricular tachycardia, or stroke) within 30 days of operation				66.4±10			to 48.2%)	
Covas [16]	25ml of Extra virgin olive oil	Changes in biomarkers of oxidative damage to lipids	6	200	2 (rather explanatory)	20-60	Normal healthy, non-smokers checked with clinical record, physical exam, blood pressure normal, normal blood test results	10 mnths: September 2002 through June 2003	Oxidative stress markers decreased linearly with increasing phenolic content. Mean changes for oxidized low-density lipoprotein level were P = 0.014 – 3.21 U/L (-5.1 to -0.8 U/L) for the high-polyphenol olive oil.	Values are means ± SD , n=12 for each group

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
Bogani [26]	50ml Extra virgin olive oil together with 150g of potatoes	Composite – blood anti-inflammatory markers (TXB2 and LTB4) and oxidative stress markers	1	12	1 (very explanatory)	25 ± 3	normolipedemic healthy subjects	Unclear 2005 – 2 weeks run in period plus 1 day	At 2 hours (P = 0.006) increase in antioxidant capacity after consumption of EVOO, difference in serum antioxidant capacity between EVOO and Corn Oil group (P=0.013)	Unclear
Dorman [27]	administration of nicardipine or nitroprusside	Rapidity and variability of blood pressure control	1	60	3 (= explanatory/ pragmatic) to 4 (rather pragmatic)	70±10 nicardopine (NIC)/ 67.3±10 Nitroprussid e (SNP)	preoperative BP NIC 155±24 SNP 159±21/ NIC 75±10 SNP 80±10 diastolic	10-month 1995-1996	Nicardipine: Therapeutic response approx. 15min; Nitropruss: Therapeutic response approx. 60mins (more variation) $p < 0.01$	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
Halpern [28]	administration of iv nicardipine or sodium nitroprusside	BP/Heart Rate; Therapeutic response rate	6	139	2 (rather explanatory)	55-75	systolic NIC 151±2 & SNP 151±3; NIC 81±2 & SNP 78±2 diastolic	14 months June 1988 to July 1989	Cardiac surgery [n=51] Nicardipine: Therapeutic response 14.0±1.0[SEM] mins [n=51] Nitropruss: Therapeutic response 30.4±3.5 min (p=0.0029)	Mean ± SEM
Goy [29]	Stents during angioplasty – Siromulus	Reduction in major cardiac events (MACE)	1 (Switzerland)	202	4 (rather pragmatic)	63-65 ± 10	Requirement Percutaneous Coronary Intervention (PCI)	6 months	MACE Events Siromulus (6/102); Events Paclitaxel (4/100) RD 1.88. Measured at 6 months	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
Morice [30]	Stents during angioplasty – Siromulus	Reduction in major cardiac events (MACE)	19	238	1 (very explanatory)	60.7±10.4	Requirement Percutaneous Coronary Intervention (PCI)	12 months	MACE Events Siromulus (7/120); Events normal (34/118) RD -22.98%. Measured at least 6 months – average 7 months±2.	Unclear
Kaiser [31]	Stents during angioplasty	Reduction in major cardiac events (MACE)	1	826	4 (rather pragmatic)	64±10	Required PCI and stenting	12.5 months: May 5, 2003 to May 31, 2004	RD -3.56 % (p=0.02) OR 0.56 (95% CI 0.35 – 0.91)	Unclear
Grube [32]	Stents during angioplasty TAXUS (Paclitaxel release)	Reduction in major cardiac events (MACE)	3	61	2 (rather explanatory)	TAXUS: 66±6.8 NIR: 63.8±7.8	Single de-novo or target lesions	6 months: Between October 2000 and March 2001	RD -6.67 % (NS)	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
Kedhi [33]	Paclitaxel releasing stents during angioplasty (comparison everolimus)	2ndry outcome used: MACE 12 months	1	1800	4/5 (very/rather pragmatic)	63.6 (55.7-72.9) Paclitaxel: 62.9 (55.4-71.1) Everolimus	Coronary artery disease	18 months: February 2007 to September 2008	Paclitaxel 8% vs Everolimus-eluting stents 5%: RD 3.29% p = 0.005	Unclear
Grube [32]	Paclitaxel releasing stent during angioplasty (comparison bare metal stent)	Reduction in major cardiac events (MACE)	3	61	2 (rather explanatory)	TAXUS: 66±6.8 BMS: 63.8±7.8	Single de-novo or target lesions	12 months: Between October 2000 and March 2001	RD -6.67 %	Unclear
Koren [34]	Arorvastatin maximum dose 80mg/day titrated to LDL-C goals of < 80 mg/dl (2.1 mmol/l)	% reduction in LDL-C levels	16	2442	Rather pragmatic	Arvorvastatin 61.6 (9.0); Usual care 61.3 (8.6)	Known CHD defined as a history of acute myocardial infarction (> 3 months	3 years – July 1995-June 1998	Mean change 34.3% (p <0.0001) RD 0.92%	LDL-C Levels mean ± SD

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
							before screening), PCTA (> 6 mths before screening), coronary artery bypass graft surgery (> 3 mths before screening), unstable angina (> 3 mths before screening)			
Jones [35]	Arorvastatin 10, 20, 40, 80 mg compared with simvastatin, pravastatin, lovastatin and fluvastatin	Mean change in plasma LDL cholesterol from baseline to the end of treatment (8 wks).	34 sites	534	Rather explanatory	55	17% patients had CAD	8 weeks;	Mean change 38% (p = 0.0001) RD 12.5%	± SD

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
Piller [36]	Doxazosin compared with Lisinopril (10-40mg/d), amlodipine (2.5-10mg.d)	CVD mortality (death due to CHD, Stroke, HF, or other CVD).	623	32804	Rather pragmatic	66.7 HF (7.6)	High risk hypertensive patients, BP > 140mm Hg and/or diastolic BP of 90mm Hg or higher, and/or taking antihypertensive medication (< 3 drugs) with a BP of 160/100 mm Hg and had at least one additional CHD risk factor	February 23rd 1994 to 31st 2002 - Active follow up. Then databases until Dec 2006 – 4 years.	RD -0.39% (doxazosin vs Lisinopril and amlodipine)	HR 3.81 (3.29-4.41), p<0.001
Grimm [37]	Doxazosin (2-16mg) compared with hydroclorothiazide	Composite: blood pressure, biochemistries, lipids/lipopr	2 Minneapolis and Chicago	107	Rather explanatory	56.3	Baseline severity: DBP ≥ 96 mm Hg and < 110 mm Hg	8 weeks?	doxazosin lowered (-19 and -16 mm Hg); HCTZ (-22 and 15 mm	SE

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
	(chorthalidone 5-50mg)	oteins, quality of life, ambulatory electrocardiograms, echocardiograms, adverse experiences, and drug adherence							Hg)	
Schiariti [38]	high dose tirofiban 25µg/kg bolus followed by 0.15 µg/kg per min for 18 hour infusion; comparator = double bolus eptifibatide 180µg/kg bolus, followed by 2µg/kg per min 18-h	Incidence of composite ischaemic events within one year	1	675	Pragmatic	62±11	Coronary Ischaemia that requires Percutaneous Coronary Intervention	24 months: February 2005 and March 2007	Effect size within 1 year 9.1% tirofiban group and 12.2% in eptifibatide group (P=0.22)	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
	infusion and 10min after 2nd 180 µg/kg bolus,									
Topol [39]	Tirofiban bolus 10 µg per kilogram of body weight followed by and infusion of 0.15 µg per kilogram per min for 18-24 hours; comparator = abciximab bolus 0.25mg per kg, followed by infusion0.125 µg per kg per min (12 hours).	MACE within 30 days of index procedure - PCI	149	2647	Explanatory	62±11	Coronary Ischaemia - Requirement PCI	Nearly 8 months: December 30th 1999 to August 25th 2000	Effect size 30 days – 7.6% tirofiban group and 6.0% in abciximab group; Hazard ratio 1.26; 95% CI	(1.01 to 1.57); P=0.038
Smits [40]	Paclitaxel stent (comparison Everolimus	Composite of all death, nonfatal MI,	1	1800	Pragmatic	PES 63.6; EES 62.9	High number of patients with acute	2 years; February 2007 to	Paclitaxel stent vsEverolimus stent: RD 2.95	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
	stent)	and TVR at 12 months.					coronary syndrome (59% PES vs 60% EES), most lesions complex	September 2008	(p = 0.02) Iry outcome RR 0.66; 95% CI	(0.50-0.86)
Grube [32]	Paclitaxel releasing stent during angioplasty (comparison bare metal stent)	Reduction in major cardiac events (MACE)	3	61	2 (rather explanatory)	TAXUS: 66±6.8 BMS: 63.8±7.8	Single de-novo or target lesions	12 months: Between October 2000 and March 2001	RD -6.67 %	Unclear
Suh[14]	Drug - Cilostazol (loading dose 200mg, then 100mg BD for 6 months)	Composite of major adverse cardiovascular events, cardiac death, non-fatal MI, clinically	5	960	Explanatory	64	Coronary artery disease Baseline severity: Intracoronary drug-eluting stents (DES)	30 months: September 2006 to June 2009	RD -0.64% p=0.73	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
		driven target lesion revascularization (TLR) and ischemic stroke at 6 months								
Douglas [41]	Intervention = clopidogrel 75mg so TAT (asprin, clopidogrel and ccilostazol 100mg BID); comparator = DAT (dual antiplatelet therapy) aspirin and clopidogrel	minimal luminal diameter of the first lesion	19	705	Pragmatic	60 (10)	Narrowing in native arteries after successful coronary stent implantation	18 months: November 2001 and April 2003	RD -0.05% p=0.89	± SD
Van Birgelen	Drug - Zotarolumus-	Acute coronary	1	1391	4 (rather	64.2 ± 10	coronary syndromes	15 months:	RD 0.11% p=94	Unclear

Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
[42]	eluting Resolute stents	syndromes at 12 months			pragmatic)		undergoing PCI and stent insertion	June 2008 - August 2010		
Serruys [43]	Intervention = Zotarolimus-eluting stents; comparator = Everolimus-eluting stent	Target-lesion failure - composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a non-target vessel) or clinically indicated target-lesion revascularisation at 12 months	22	2292	5 (very pragmatic)	64.2 ± 10.8	stable coronary disease or acute coronary syndromes Baseline severity: Requiring stents	6 months: April 30 2008 to October 2008	RD -0.57% p=0.66	Unclear
Zhu [44]	Intervention = 10mg	Achieving European	152	1215	4 (Rather	60-62 (9.3-	Fasting LDL-Cholesterol of	unclear	RD 17.16% (p <	Unclear

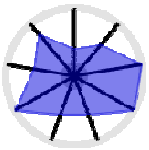
Study	Intervention	Primary outcome	No. of centres	Sample size (number rand'd)	Degree of pragmatism	Participant Age –Mean (SD)	Participant baseline severity	Duration of trial	Effect sizes Risk Difference (RD) if possible.	Measures of variance for primary outcome
	rosuvastatin; comparator = 10mg arorvastatin	LDL-C goal (<3.0 mmol/l) at week 12			pragmatic)	9.7)	>3.5 mmol/l if untreated or fasting LDL-C of >3.1 mmol/l if currently being treated with start dose of other lipid lowering therapy.		0.001)	
Olsson [45]	Intervention = 10mg rosuvastatin; comparator = 10mg arorvastatin	LDL-C reductions	6	412	1 (very explanatory)	56-58 ± 10	Hypercholesterolemia Baseline severity: LDL-C 160 and <250mg/dL	52 week: 1999 to 2000	Reduction in LDL-C 46% 5mg and 50% 10mg vs 39%, both P < 0.001	Unclear

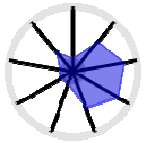
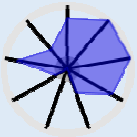
Table 8.2 Comparison of 14 matched pairs of pragmatic and explanatory trials of cardiovascular trials.

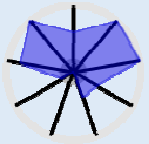
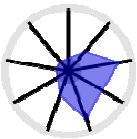
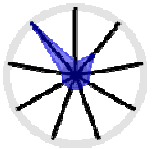
Duplicate entry ST six trials

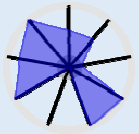
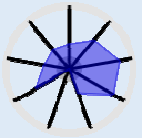
The latter two were not always possible, which meant a comparison of estimates of treatment effect was not possible. A Cochrane Risk of Bias assessment [113] was possible, which is shown here.

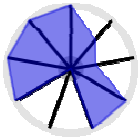
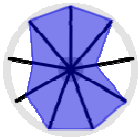
Each pair of matched trials are grouped by row colour: white or shaded. The degree to which a trial was pragmatic or explanatory varied considerably; some pragmatic/explanatory trials were much more pragmatic/explanatory than others.

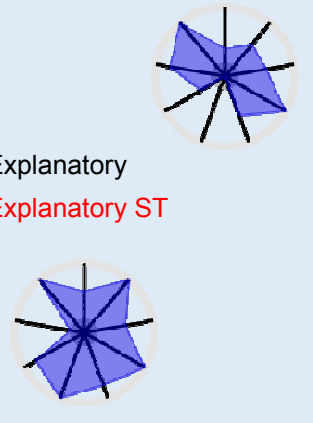
Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Bots [177] Intervention = Rosuvastatin 10mg; comparator = arorvastatin 10mg, simvastatin 20mg, pravastatin 40mg,	Unclear Unclear	Unclear Unclear	Low risk (open label – intention of researchers to test usual care in primary care setting Unclear	Low risk Low risk	Low risk Low risk	Unclear - Analysis not per-protocol intention to treat, but changed during study to add additional analysis. Low risk	Unclear Unclear	 Pragmatic Pragmatic ST 

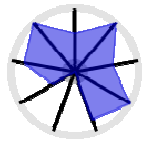
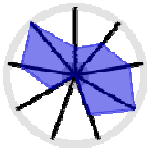
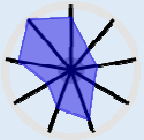
Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Davidson [178] Intervention = Rosuvastatin 5mg or 10mg ; comparator = arorvastatin 10mg,	Unclear Unclear	Unclear Unclear	Unclear Low risk	Low Risk High risk	Low risk Low risk	Unclear (violations leading to exclusion, deviations leading to exclusion, withdrawals) all detailed and adverse events Low risk	Unclear High risk	 Explanatory Explanatory ST 
Brady [163] Intervention = oral metoprolol 50mg twice daily, supplemented by IV doses when necessary; comparator = placebo	Low risk: Randomisation at TheSealedEnvelope.com Web site p603	Low Risk: Treatment allocated in a 1:1 ration by using random permuted blocks of size 2, 4, 6 within 4 stratification factors p603	Low risk: Patients, doctors, medication identical appearance numbers for ID purposes for patient and drug. No evidence unblinding occurred. Unclear about outcome assessment but says DMEEC blinded comparison p603	Low risk	Low risk	Low risk	Low risk	 Pragmatic

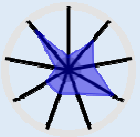
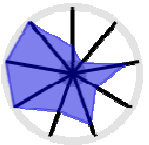
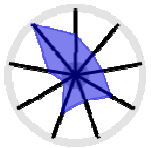
Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Yang [166] Intervention = metoprolol 100mg; comparator = placebo	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Explanatory 
Covas [169] Intervention = olive oil high phenolic content (virgin olive oil) 2.7mg/kg; comparator = olive oil moderate and low phenolic content	Low risk (taken from a latin square for each centre by blocks of 42 participants (14 people in each sequence) using specific software was that was developed at the Institute Medical Research, Barcelona, Spaion p335	Low risk – faxed to participating centres upon request for each individual	Low risk code number for treatment containers concealed from participants and investigators only disclosed after analyses.	Low risk	Low risk	Unclear: Couldn't assess potential interactions between other dietary constituents, self reporting of diet, full consumption of oil treatment, short treatment period	Low risk	Pragmatic 
Bogani[179] Intervention = extra virgin olive oil; comparator = oilive and corn oil	Low risk, latin square design	Unclear	High risk, un-blinded for men, investigators and outcome assessors	Low risk	Low risk	High risk – self selected group, all men.	Unclear	Explanatory 

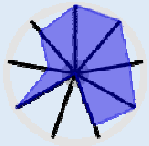
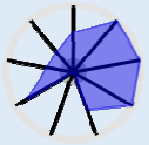
Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Dorman [180] Intervention = nicardipine; comparator = nitroprusside	Unclear - Randomisation by investigation pharmacy 17p	Unclear	Low risk – both covered with foil so appeared identical to nurse who was also measuring outcomes p17	Low risk	Low risk	Unclear	Unclear	Pragmatic 
Halpern [181] Intervention = nicardipine; comparator = nitroprusside	Unclear Randomisation was by pre-assigned entry number without regard to the type of surgical procedure performed P1638	Unclear	High risk A coded open label solution was prepared. Sodium nitroprusside solution was wrapped in an opaque material to prevent denaturation by light	High risk - Not ITT, only adverse effects for all 139 patients, 3 excluded from analysis regarding results of maintenance therapy and 22 excluded from analysis at therapeutic response	Low risk	Unclear	Unclear	 Explanatory

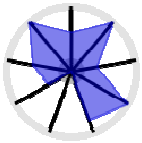
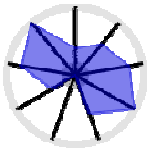
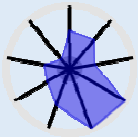
Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Goy [182] Intervention = paclitaxel-eluting stents; comparator = sirolimus-eluting stents	Unclear UNCLEAR	Unclear UNCLEAR	Unclear UNCLEAR	Low risk Low risk	Low Low risk	Unclear Low risk	Unclear UNCLEAR	Pragmatic  Pragmatic ST 
Morice[183] Intervention = paclitaxel-eluting stents; comparator = standard uncoated stents	P1174 Low risk - codes for random assignments to the treatment groups were generated by computer in blocks of four Low risk	P1174 Low risk - distributed in sealed envelopes to each participating center. Low risk	P1174 Low risk. Double blind - The sirolimus-eluting stents were indistinguishable, except under a microscope, from the uncoated stents. Outcome assessment central adjudication. Low risk	Low risk Low risk	Low risk Low risk	Low risk Low risk	Low risk Low risk	Explanatory  explanatory ST 

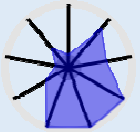
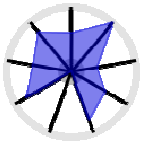
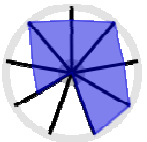
Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Kaiser [184] Intervention = Sirolimus-coated Cypher or paclitaxel-coated Taxus drug-eluting stents; comparator = cobalt chromium-bare metal Vision stents	Unclear how patients randomised- The operator in charge enrolled all patients being treated with PCI and stenting, and patients were randomised at midnight at the beginning of each day's clinic to one of the three stent types by use of sealed envelopes. Low risk	Low – sealed envelopes Low risk	Low risk – patients knew and so did surgeons. Unlikely to have effect on outcome. All outcome events were adjudicated by an independent Critical Events Committee blind to the stent type used. Low risk	Low risk Low risk	Low risk Low risk	Unclear Low risk	Low risk Low risk	
Grube [185] Intervention = everolimus-eluting stents; comparator = bare metal stents	Unclear Unclear	Unclear Unclear	Strictly double blinded analysis. To maintain blinding packaging, stents were indistinguishable by physical and radiographical appearance. Cath labs and clinical events committee blinded to treatment groups Low risk	Low risk Low risk	Low risk Low risk	Low risk High risk	Low risk High risk	

Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Kedhi [186] Intervention = everolimus-eluting stents; comparator = paclitaxel-eluting stents	Low risk - Computer generated p201	Low risk - Sealed, opaque sequentially numbered allocation envelopes AFTER passage of guide wire	Patients didn't know WHICH stent	Low risk	Low risk	Unclear	Low risk	 Pragmatic
Grube [185] Intervention = everolimus-eluting stents; comparator = bare metal stents	Unclear	Unclear	Strictly double blinded analysis. To maintain blinding packaging, stents were indistinguishable by physical and radiographical appearance. Cath labs and clinical events committee blinded to treatment groups	Low risk	Low risk	Low risk	Low risk	 Explanatory
Koren[187] Intervention = arorvastatin max dose 80mg/day; comparator = usual care – any treatment deemed appropriate by physician	Unclear – randomisation by central laboratory	Unclear	Low	Low - An independent outcomes committee of five cardiologists reviewed and adjudicated all study outcomes.	Low risk	Unclear - Privacy issues contributed to difficulties with follow up information data that would not have occurred had the study been performed entirely in a Research setting. Recruitment was through databases so no relationship with doctors and patients pre-existed.	Unclear	 Pragmatic

Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Jones [188] Intervention = arorvastatin 10mg, 20mg, 40mg and 80mg; comparator = simvastatin 10, 20, 40mg, provatatin 10, 20, 40mg, lovastatin 20, 40, and 80mg and fluvastatin 20, 40mg	Unclear	Unclear	High Risk	Unclear	Unclear	Unclear	Unclear	 Explanatory
Piller [189] Intervention = calcium channel blocker -amlodipine (2.5-10mg/d) and angiotensin converting enzyme inhibitor Lisinopril (10-40mg/d); comparator = chlorothiadone (12.5-25mg/d)	Unclear, looked at protocol and DSMB will monitor recruitment to decide	Central allocation - Called up Clinical Trials Centre to get randomisation p347	Blinding but choice of primary outcome (mortality) should prevent bias p 345 [190] Davis et al)	Problems with Canadian centres no access to database to assess outcomes.	Does not appear to be selective	Final stopping rule, used in one of the arms.	Low risk	 Pragmatic
Grimm [191] Intervention = diuretic hydrochlorothiazide (HCTZ) (Chlorothiadone) 25-50mg; comparator = α_1 antagonist - doxazocin (2-16mg)	Low risk - Randomization was carried out by a computer-generated, coded list, which was stratified by clinic site.	Unclear	Low risk. Participants blinded and doctors added drug to study drug in blinded fashion, measurements done by individuals who appear to be blinded as well.	Low risk	Low risk	Unclear	Low risk	Explanatory 

Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Schiariti [192] Intervention = high dose tirofiban 25µg/kg bolus followed by 0.15 µg/kg per min for 18 hour infusion; comparator = double bolus eptifibatide 180µg/kg bolus, followed by 2µg/kg per min 18-h infusion and 10min after 2nd 180 µg/kg bolus,	Low risk - Block randomisation scheme, 75 blocks of five and 75 blocks of four patients.	Unclear	Low risk - Open label, an external reviewer unaware of treatment assignment coded all events.	High risk – as treated analysis rather than ITT	Low risk	Unclear	Unclear	Pragmatic 
Topol [193] Intervention = Tirofiban bolus 10 µg per kilogram of body weight followed by and infusion of 0.15 µg per kilogram per min for 18-24 hours; comparator = abciximab bolus 0.25mg per kg, followed by infusion0.125 µg per kg per min (12 hours).	Low risk – use of a central interactive system.Patients randomised on the basis of prior angiographic findings before intervention was begun.	Unclear	Low risk - Double blind and remained blinded until primary end points finalised and entered. Outcome assessment by	Low risk - ITT	Low risk	Low risk	Low risk	Explanatory 

Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Smits [194] Intervention everolimus-eluting stents; comparator = paclitaxel-eluting stents	Low risk - computer-generated random numbers.	Low risk - using sealed, opaque, sequentially numbered allocation envelopes after passage of the guide wire.	Low risk – could not blind surgeons, blinded outcome assessment. Patients did not know either.	Low risk	Low risk	Unclear	Low risk	 Pragmatic
Grube [185] Intervention = everolimus-eluting stents; comparator = bare metal stents	Unclear	Unclear	Strictly double blinded analysis. To maintain blinding packaging, stents were indistinguishable by physical and radiographical appearance. Cath labs and clinical events committee blinded to treatment groups	Low risk	Low risk	Low risk	Low risk	 Explanatory
Suh [168] Intervention = cilostazol 200mg and 100mg twice daily so TAT (asprin 300mg, clopidogrel 300-600mg and ccilostazol); comparator = DAT (dual antiplatelet therapy) aspirin and clopidogrel	Unclear	Unclear	Unclear. Open label trial. Blinded evaluation. Possible bias related to treatment Target legion revascularisation (TLR)	High risk. Intention to treat but was actually "as-treated" as did not analyse all randomised.	Low risk	Unclear	Unclear	 Pragmatic

Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Douglas[195] Intervention = clopidogrel 75mg so TAT (asprin, clopidogrel and ccilostazol 100mg BID); comparator = DAT (dual antiplatelet therapy) aspirin and clopidogrel	Unclear – p2826. The coordinating center developed a randomization scheme.	Low risk matching unmarked bottles of 50 mg cilostazol and placebo were prepared with a patient allocation number. Each site received a list of sequential allocation numbers.	Unclear, patients and doctors blinded so double blinded but no mention if blinding successful - Outcome assessment independent	High risk - Outcome data for all patients who had angiography at 6 months but that was only 74.6% of patients so “as-treated" analysis performed	Low risk	Unclear	Unclear	 Explanatory
von Birgelen [196] Intervention = Zotarolimus-eluting stents; comparator = Everolimus-eluting stent	Low risk – p1351 computer-generated random numbers (block stratified randomization version 5.0 by S. Piantadosi)	Low risk – p1351 sealed opaque sequentially numbered allocation envelopes after passage of the guidewire or pre-dilation if necessary	Low risk p1352 Patients no knowledge of the stent type allocated to (single blinded design). Follow up and outcome assessment blinded. Central adjudication.	Low risk	Unclear did not pre-specify all subgroup analysis.	Low risk	Low risk	 Pragmatic
Serruys [197] Intervention = Zotarolimus-eluting stents; comparator = Everolimus-eluting stent	Unclear	Unclear	Low risk. Patients blinded, stents so unlikely be able to find out. Surgeons knew. Subgroups unknown to outcome adjudicators.	Low risk	Unclear	Low risk	Unclear	 Explanatory

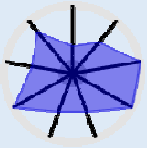
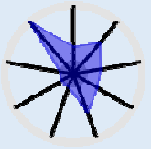
Trial	Random Sequence generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias	PRECIS wheel
Zhu[198] Intervention = 10mg rosuvastatin; comparator = 10mgarorvastatin	Unclear	Unclear	Low risk (open label – intention of researchers to test usual care in primary care setting	Low risk	Low risk	Unclear - Analysis not per-protocol intention to treat, but changed during study to add additional analysis.	Unclear	 Pragmatic
Olsson[199] Intervention = 10mg rosuvastatin; comparator = 10mgarorvastatin	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear	Explanatory 

Table 8.3 Risk of Bias Domain descriptions for all trials included in the Cochrane Review on hypertension

Duplicate entry ST four trials

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
1	**ATTMH[23]** **High-dose thiazide**	Unclear Unclear mention randomly allocated randomisation code	Unclear Unclear randomisation code	Low Unclear Patients blinded – identical tablets, health care providers not blind. blind outcome assessment	High Unclear Same number lost to follow up in active as in placebo groups. Reasons for stopping same. “On treatment” as well as ITT but no adjusted rates data in article. Third patients prematurely stopped treatment randomised to but similar in active and placebo. More withdrawals by doctors in placebo. (195 vs 110). No attempts made to correct for such bias.	Low Unclear	High Unclear Stopped early due to data dependent process. A lot of discussion about Australian trial results and retrospective analysis	High Unclear
2	**Barraclough[19]** **High-dose thiazide**	Low Appears to be block randomisation	Unclear No mention of allocation	High risk Doctor knew. Not clear if patient	High risk Withdrawn if poor attendance, 17	Low Low risk	High Groups do not appear to be similar	High High risk

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
		"allocated at random, series balanced for age and sex after every 10 allocations" Unclear	concealment at all. Unclear	blinded. No discussion of blinded outcome – assumption dr took BP. Low risk	withdrawn medical reasons and 19 left for non-medical reasons out of total of 58. Not balanced between control and treatment groups. High risk		at baseline when mean weight, blood urea, source compared, no info on statistical significance. One patient each group had ECG abnormalities and none had evidence of probable coronary disease. More abnormalities in control group. Unclear	
3	**Carter [48]** **High-dose thiazide**	Unclear	Unclear	High risk No mention of blinding for patients, doctors or outcome assessment	Low risk "Of the 99 patients in the trial, 2 have been lost to follow up..."	Unclear	Low risk Groups similar at baseline, ITT Stopped early as unethical to continue.	Unclear
4	**Dutch TIA [49]** **Beta blocker**	Low Random permuted blocks Low	Low Blinded randomisation codes were distributed by telephone Low	Low risk Double blinded - patients identical placebo appearance and taste to active tablets. Outcome independently assessed without knowledge of	Low risk No patients lost to follow up. ITT Low	Low risk Low	Low Low	Low risk Low

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
				treatment allocation. Low				
5	**EWPHBPE [50, 51]**	Unclear Not mentioned	Low Individually sealed envelope	Low risk Triple blinded. Numbered drug containers so doctors, patients and outcome assessment blind to allocation.	Unclear 128 out of 840 patients (15,2%) were lost to follow up but unclear if even numbers in control and treatment group. ITT	Unclear Patients were censored if they had "one of the specific study terminating events, including death, non-fatal cerebral or subarachnoid haemorrhage, development of hypertensive retinopathy grade III or IV, dissecting aneurysm, congestive heart failure not controllable without diuretics or antihypertensive drugs, hypertensive encephalopathy, severe increase in left ventricular hypertrophy, and a rise in blood pressure exceeding the defined limits."	Low risk	Unclear
6	**HOPE HYP[52]**	Low	Unclear	Low risk	Low	Unclear	Low risk	Low risk

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
	ACE inhibitors	Two by two factorial randomised	Not mentioned	Double blind and Independent outcome assessment	99.9% of patients followed up (9535/9541 randomised patients)	No protocol available and no duplicate data extraction in previous Cochrane reviews	ITT	
7	**HSCSG[53]** **High-dose thiazide**	Unclear	Low Sealed envelope	Low risk Doctor and patient blinded and independent assessment of outcomes without being aware of randomisation	Unclear 40 patients rejected but does not mention number lost to follow up	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	Low risk	Unclear

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
8	**HYVET[20]** **Low-dose thiazide**	Low risk Permuted blocks of 4 and 6 of any 10 patients were used to ensure roughly equal assignment to each of the two groups within large centres. Low	Low risk An interactive voice response system (IVRS) is employed to tell the investigator which 6-month drug pack to prescribe. Unclear	Low risk The main trial is a randomised, double-blind, placebo-controlled trial. “All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol.” Unclear	Unclear Randomised 1845 Reported on the number of patients lost to follow-up (16 patients) "...vital status was unknown in 17 patients..." High risk	Unclear Cannot extract the number of patients in each group that had a non-fatal myocardial infarctions. Correspondence with the author: "The serious adverse events noted in the publication...are the numbers the total serious adverse events OR was the first event counted and analyzed? **Answer: It is the total number of SAEs. Patients could contribute more than one SAE."** Correspondence with the author: "If a patient had an event after being censored were those events counted? If not, is it possible to see that data? **Answer: It would depend on the event. If**	Low risk ITT High risk	Unclear High risk

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
						it was a recurrent endpoint then it was not counted (e.g. a further non-fatal stoke). If the event was a new endpoint (e.g. a fatal MI in someone who had previously had a non-fatal stroke) then it was." Unclear		
9	**HYVETpilot [54]** **Low-dose thiazide** **ACE inhibitors**	Low risk "The unit of randomization was the individual and the SAS Random Allocation of Treatments Balanced in Blocks Program was used to generate the schedule."	High risk	High risk No blinding – open design	Low risk "Of the 1283 patients who were assigned to groups, only 27 (2.1%) were lost to follow-up (had no end-of-trial information)." "Of the 426 patients allocated randomly to a diuretic-based treatment, 385 (88.5%) were alive and provided information at the end of the trial. The corresponding numbers were 397 (89.8%) for ACE based treatment and 394	Low risk As this was an open study, the randomized treatment could be continued after a non-fatal event."	Unclear	Unclear

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
					(90.1%) for no treatment."			
10	**MRC-O[55]** **Low-dose thiazide** **Beta-blocker**	Low risk Randomisation was in stratified blocks of eight within each sex and clinic.	Unclear Methods not adequately described	Low risk Patients blinded, but providers not blinded. Blind outcome assessment	High risk Loss to follow-up (25%). Missing data may be due to side effects. Beta blocker more than diuretic for major side effects and inadequate BP control. No imputations.	Low risk All outcomes were reported as stated in the protocol.	Unclear risk Other antihypertensive drugs added to randomly allocated treatment to control blood pressure. The observed effects may equally have resulted from the different additional drugs.	Unclear
11	**MRC-TMH [56]** **High-dose thiazide** **Beta-blockers**	Low risk Stratified blocks of 8 within each sex, 10 year age group and clinic	Unclear No information in the text	Low risk Doctors not blind, only patients, blind outcome assessment.	Unclear 19% lost to follow up	Unclear	Low risk Groups similar at baseline, ITT	Unclear
12	**Oslo [57]** **High-dose thiazide**	Low risk Random numbers table	Unclear No information	Unclear Blind outcome assessment by two independent cardiologists. No statement by authors	Low risk None lost to follow up	Unclear No protocol available and no duplicate data extraction in previous Cochrane	Low risk No difference between groups,	Unclear

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
				that patients and doctors not blinding and if they perceived this had an effect.		reviews		
13	**PATS [58]** **Low-dose thiazide**	Unclear "patients entered into active or placebo group according to order of envelopes" – unclear how that order was created.	Low risk Ordered sealed envelope system	Low risk Double blind	Unclear No difference in numbers who dropped out in placebo and active groups due to non-medical reasons not clear if these people were followed up but states "patients withdrawn from the trials were followed up to make an intention to treat analysis	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	Low risk No difference in patients at baseline, ITT	Unclear
14	**SHEP[59, 60]** **Low dose thiazide**	Low risk Blocked randomisation	Low risk "Each randomization was carried out by telephone"	Low risk Described as double-blind and outcome assessment also blinded	Low risk "We specified an "intention to treat" rule (with study groups divided by the randomized assignment regardless of subsequent crossovers) and a plan for replacing any	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	Low risk ITT	Low risk

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
					missing annual visit BP with the last available value			
15	**SHEP-P [61]** **Low dose Thiazide**	Unclear No information	Unclear No information	Low risk Double blind. Outcome assessment also blinded.	Unclear No information	High risk "For any participant who had two or more events, one was designated the study event based on a hierarchical classification headed by death followed by four categories of nonfatal events in rank order of stroke, other hypertensive events, atherosclerotic events, and noncardiovascular events. When there were two events in one category, the event that occurred first was used."	Low risk ITT and no difference at baseline	Unclear
16	**SYST-EUR [62]** **Calcium Channel Blockers**	Low risk "randomized to double-blind treatment with active medication or	Unclear No information	Low risk Double blind and blinded outcome assessment	Low risk "For patients who withdrew from treatment for whom regular follow-up was	Unclear No protocol available and no duplicate data extraction in previous Cochrane	Low risk ITT and no difference at baseline	Low risk

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
		placebo by means of a computerized random function"			not possible, we annually collected information on vital status, occurrence of major endpoints and other events, and the use of antihypertensive medications (non-supervised open follow-up). Patients without any report within the year before the trial stopped were counted as lost to follow-up."	reviews		
17	**TEST [21]** **Beta blockers**	Low risk Computer generated random scheme using a random permutated block design with a block size of four was used for randomisation, stratified for centre, age and Scandinavian treatment score.	Unclear No information	Low risk Double blind. Independent end-point committee reviewed fatal end-point.	Low risk Treatment discontinued in 10% and all patients followed up regardless of withdrawal or not.	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	Low risk No difference in patients at baseline, ITT	Unclear
18	**UKPDS 39[63]** **Beta blocker**	Low risk Computer-generated	Low risk “Allocation	High risk Patients not blinded;	Unclear Not indicated whether	Low risk All outcomes were	Unclear Other	Unclear

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
	ACE Inhibitors	random sequence but not blocked so slight difference in numbers of patients allocated to treatments.	concealment was done with opaque, sealed envelopes with a check maintained on numerical sequence, until dates of opening and results"	providers not blinded. There was no blinding of outcome assessment, but the outcome assessed (i.e. death) is unlikely to be influenced by lack of blinding.	reasons for missing outcome data were similar across treatment groups	reported as stated in protocol.	antihypertensive drugs added to randomly allocated treatment to control blood pressure. The observed effects may equally have resulted from the different additional drugs.	
19	**USPHSHCSG [64]** **High dose thiazide**	Unclear No information	Unclear No information	Unclear Double blind, no information on outcome assessment	High risk Dropouts 132 (33.9%) of whom 75 have been lost to regular follow up (~17%), vital status of 26 of dropouts is unknown. No differential drop out rate between treatment and control groups and similar lack of vital status for both groups.)	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	High risk Per treatment analysis, similar at baseline.	High risk
20	**VA-1[65]** **High dose thiazide**	Low risk Table of active numbers	Low risk Sealed envelope used to assign randomisation to active antihypertensive medication or	Low risk Double blind. Unclear how outcome assessment was carried out.	Low risk Total number of drop outs 12 out of 143 or 8.4%. Divided equally between placebo and active patients.	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	Low risk Similar at baseline.no statistically significant differences.	Low risk

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
			placebo				ITT	
21	**VA-11 [66]** **High dose thiazide**	Low risk Table of active numbers	Low risk Sealed envelope used to assign randomisation to active antihypertensive medication or placebo	Low risk Double blind. Unclear how outcome assessment was carried out.	Unclear Total number of drop outs 56 out of 380 or 15%. Divided equally between placebo and active patients but don't know reason for 24. Possible that reason for missing outcome data may be related to true outcome as 3 of the patients in placebo group non-terminating morbid events prior to their dropping out.	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	Unclear Similar at baseline.no statistically significant differences. Not ITT.	Unclear
22	**VA-NHLBI[67]** **High dose thiazide**	Unclear Randomisation by next unused therapy number from a list supplied by the data centre	Low risk Drugs unique therapy number	Low risk Double blind. Outcome assessment may be blinded but unclear.	High risk Total number of drop outs 98/508 (19%) active group and 104/504 (21%) placebo group.	Unclear No protocol available and no duplicate data extraction in previous Cochrane reviews	Unclear Not clear if groups similar at baseline	Unclear
23	**Wolff [22]**	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk

Trial	Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources bias	Overall Risk of Bias
	High dose thiazide	Table of random numbers	Coded drugs	Double blind. Outcome assessment may be blinded but .unclear	10 patients in drug group and 1 in placebo group absent and stopped attending clinic. ie 6 out of 10 followed up by nurses and "delinquent for social rather than medical reasons. None admitted any increase in symptoms suggested of treatment failure."	No protocol available and no duplicate data extraction in previous Cochrane reviews	Appear similar at baseline of groups. Results for all 87 patients presented, ITT	

Table 8.4 with PRECIS-2 scores for each domain in HYVET [21] - Treatment of Hypertension in Patients 80 years of age or older (more explanatory trial)

	Domain	Score	Rationale
1	**Eligibility Criteria**	**1**	Not usual care – focussing on older people - those 80 years of age or older and had a sustained systolic blood pressure of 160mm Hg or more. Often this group though is excluded from clinical trials. (Checked pre-trial by stopping all hypertensive treatments for at least TWO months and 2 blood pressure measurements during 2 visits, 1 month apart, after having been seated for 5 minutes. Third visit, standing blood pressure taken twice after patient standing for 2 minutes). Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive medication, a serum creatinine level greater than 150 µmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care. In usual care antihypertensives can be used by all ages – usually over 40.
2	**Recruitment Path**	**3**	Unclear but also had placebo run in period.
3	**Setting**	**5**	195 centres, in 13 countries in Europe, China, Australasia, and North Africa
4	**Organisation intervention**	**3**	Unclear - no specific mention of resources, expertise, organisation. There were issues with some centres having to be dropped as incomplete data or failure to use validated equipment or inadequate data.
5	**Flex of experimental intervention – Delivery**	**2**	Investigators could adjust the dose of the trial medication more frequently than at each visit, if desired so tailored to individual patients's needs. Patients received either indapamide (sustained release, 1.5 mg) or matching placebo alone. At each visit (or at the discretion of the investigator), if needed to reach the target blood pressure for the individuals, perindopril (2 mg or 4 mg) or matching placebo could be added. The target systolic blood pressure was less than 150 mm Hg, and the target diastolic blood pressure was less than 80 mm Hg. The use of additional antihypertensive agents for more than 3 months resulted in withdrawal of the patient from double-blind follow-up, with an option to enter open follow-up. Patients were also withdrawn from double-blind treatment if they had received the maximum dose of the study

			drugs yet had a systolic blood pressure while sitting of 220 mm Hg or more or if they had a diastolic blood pressure while sitting of 110 mm Hg or more on at least two consecutive visits that were 2 or more weeks apart.

6	**Flex of experimental intervention – Adherence**	**2**	Run-in period so exclude non-compliers thereafter does not appear to be exclusion based on compliance. Exclusion if blood pressure too high after 3 months or if had additional hypertensives for more than 3 months.
7	**Follow up**	**1/2**	Every 3 months during 1st year and at least every 6 months thereafter BP measured, for the trial period (6.5 years before terminated for ethical reasons) -10,500 patient years planned. Extensive data collection, far more than usual care which would be BP and blood tests. ECG only done in usual care if indicated as is cognitive function. Annual visits: information was collected on current diseases, medication, blood pressure, biochemical levels (sodium, potassium, urea, creatinine, glucose, uric acid, cholesterol levels (total and high-density lipoprotein), and hematologic measures (hemoglobin, hematocrit), and electrocardiography and an assessment of cognitive function with the use of the Mini–Mental State Examination were performed. If the patient was enrolled in an optional add-on study, a quality-of-life questionnaire was also completed. At the 3-month and 6-month visits, only data on current diseases, medication, and blood pressure were collected. Had to come out of trial double blind follow up if on additional treatment for hypertension for more than 3 months but could continue with open follow up.
8	**Primary Outcome**	**3**	Fatal or nonfatal stroke and centrally adjudicated. Of interest to patient but of greater interest would probably have been the secondary outcome "Death from any cause".
9	**Analysis**	**5**	ITT but also per protocol analysis

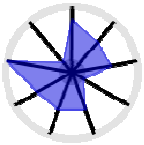
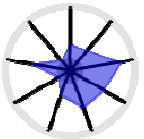
Table 8.5 with PRECIS-2 scores for each domain in WOLFF [22]- Effects of Treatment on Morbidity in Hypertension (more pragmatic trial)

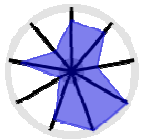
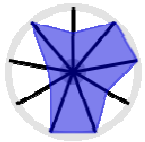
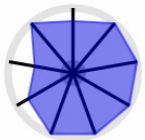
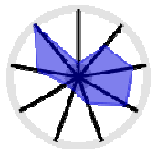
	Domain	Score	Rationale
1	**Eligibility Criteria**	4	Male and female patients, mainly black, with a diastolic BP of 100 mm Hg or more (3 separate occasions at least one week apart) after resting for 5 mins on a bed. Usual exclusions but not people already taking antihypertensives or those who have cardiovascular disease
2	**Recruitment Path**	3	Appears to referral to clinic but unclear
3	**Setting**	3	One setting but usual setting for treatment of high blood pressure - Baltimore City hospitals, USA one hypertension clinic

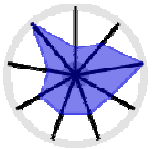
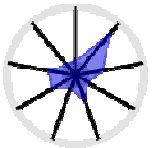
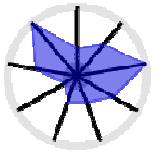
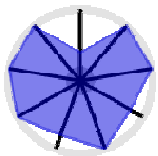
4	**Organisation intervention**	5	No additional personnel or resources or training mentioned
5	**Flex of experimental intervention – Delivery**	5	Flexible focussing on individual patient's cardiovascular symptoms. Keep regime for 3 months before changing.
6	**Flex of experimental intervention – Adherence**	5	Does not appear to be monitored or part of treatment
7	**Follow up**	5	Up to 2 years - Successive visits until stabilised, CXR and ECG every 6 months, blood, glucose levels, 3 months. Eyes and urine test, blood test every clinic visit. Routine examinations 2 month intervals but could be 1 week to 5 month intervals so appears that follow up based on individual patients.
8	**Outcome**	2	Composite outcomes – many symptomatic so patient relevant outcomes. Treatment failure eg cardiovascular accident, headache, coronary artery disease, congestive heart failure, retinopathy, clinical diabetes, deaths, increasing serum urea nitrogen and proteinuria – latter very explanatory.
9	**Analysis**	5	Results for 87 patients presented and all reasons for treatment failures, relatively small numbers and composite outcomes presented, 10 absentees in drug group but 6 out o 10 followed up by nurses and "delinquent for social rather than medical reasons. None admitted any increase in symptoms suggestive of treatment failure."

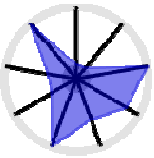
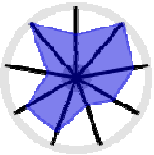
Table 8.6 23 trials in Cochrane review for internal and external validity

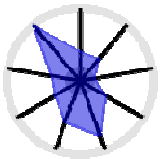
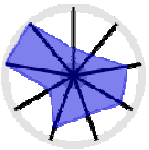
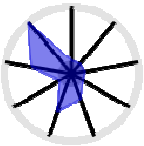
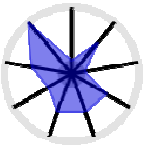
Duplicate entry ST four trials

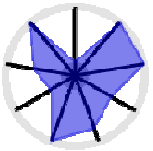
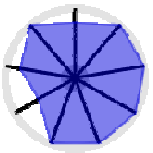
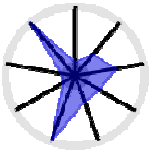
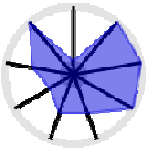
	Study	Pragmatic/ Explanatory	Effect size Risk Ratio Fixed, 95% CI	Risk of Bias (Allocation concealment)	Intervention	Outcome	PRECIS-2 wheel
1	**ATTMH [176]** **High-dose thiazide**	Explanatory Hard to say	Total mortality 0.71 (0.43-1.18)	High Unclear	Chlorothiazide 500 mg, 1000 mg, Methyldopa, propranolol, or pindolol, Hydralazine or clonidine	mortality, stroke, CHD, CHF (patients were censored after the first outcome so data is limited to first outcome in each category)	 ST "wheel" 
2	**Barraclough [172]** **High-dose thiazide**	Explanatory Explanatory	Total mortality 0.33 (0.04-3.11)	High High	Bendrofluazide (93%), Methlydopa, and debrisoquine	mortality, CHD, stroke, CHF, and diastolic BP	 ST "wheel"

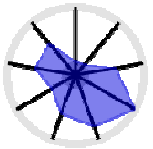
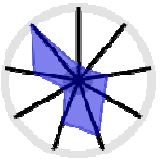
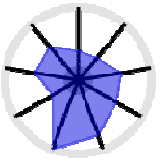
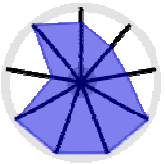
							
3	**Carter [200]** **High-dose thiazide**	pragmatic	Total mortality:0.58 (0.33-1.01)	Unclear	Thiazide, 76%, Methyldopa (0.75-2 g), bethanidine or debrisoquine	Stroke, mortality, CHD, CHF	
4	**Dutch TIA [201]** **Beta blocker**	pragmatic	Total mortality 1.12 (0.79-1.57)	Low Low	Atenolol 50 mg daily Identical placebo tablet	Mortality, CHD, stroke, total CV events,	 ST “wheel” 
5	**EWPHBPE [202, 203]**	explanatory	Total mortality 0.92 (0.76-1.12)	Unclear	HCTZ/triamterene, 25/50 mg. 1 to 2 tabs, methyldopa 0.5-2 g.	Mortality, stroke, CHD, CHF, systolic BP and diastolic BP	

6	**HOPE HYP [204]** **ACE inhibitors**	explanatory	Total mortality 0.79 (0.67-0.93)	Low	Ramipril 2.5 mg titrating up to 10 mg or placebo. Other factor was Vitamin E 400 IU/day.	Primary: composite of myocardial infarction, stroke, or cardiovascular death (total CV events). Total mortality, total stroke, total CHD.	
7	**HSCSG [205]** **High-dose thiazide**	explanatory	Total mortality: 1.01 (0.6-1.72)	Unclear	Deserpidine 1 mg plus methyclothiazide 10 mg.	Mortality, stroke, CHD, CHF, systolic BP and diastolic BP	
8	**HYVET [174]** **Low-dose thiazide**	explanatory	Total mortality 0.82 (0.69-0.99)	Low	Step 1 indapamide 1.5 mg daily. Step 2 perinodopril 2 mg daily. Step 3 perindopril 4 mg daily. Control: identical appearing placebos for each step	Total stroke, total coronary artery disease, total mortality, total cardiovascular events (including CHF)	
9	**HYVETpilot [206]** **Low-dose thiazide**	pragmatic	Total mortality 1.29 (0.77-2.16) 1.11 (0.65-	Unclear Unclear	Diuretic (usually bendrofluazide 2.5 mg), an ACE inhibitor (usually lisinopril 2.5 mg) or	Total stroke, total mortality, cardiovascular mortality, cardiac mortality, sitting systolic BP and diastolic BP.	

	ACE inhibitors		1.90)		no treatment.		ST "wheel" 
10	**MRC-O [207]** **Low-dose thiazide** **Beta-blocker**	explanatory	Total mortality 0.87 (0.72 – 1.05) 1.06 (0.90-1.27)	Unclear	HCTZ/amiloride, 25 mg/2.5 mg , atenolol 50 mg daily, or placebo	Mortality, Stroke, CHD, systolic BP and diastolic BP	
11	**MRC-TMH [208]** **High-dose thiazide** **Beta-blockers**	Pragmatic	Total mortality 1.02 (0.83 – 1.26) 0.93 (0.75-1.15)	Unclear	Bendrofluazide 10 mg daily (71% mono) , Propranolol 80-240 mg daily (78% mono) , methyldopa added if required.	Mortality, stroke, CHD, systolic BP and diastolic BP.	

12	**Oslo [209]** **High-dose thiazide**	Explanatory	Total mortality 1.04 (0.43 – 2.52)	Unclear	Hydrochlorothiazide (95%), methyldopa, and propranolol (26%).	Stroke, CHD, mortality, CHF, systolic BP and diastolic BP	
13	**PATS [210]** **Low-dose thiazide**	pragmatic	Total mortality 0.92 (0.74-1.14)	Unclear	Indapamide 2.5 mg daily Identical placebo tablet	Mortality, stroke, coronary heart disease, blood pressure	
14	**SHEP[211, 212]** **Low dose thiazide**	explanatory	Total mortality 0.88 (0.74 – 1.05)	Low risk	Chlorthalidone 12.5-25 mg (69%), Step 2. atenolol 25-50 mg (23%) or reserpine 0.05-0.1 mg. Identical placebo.	Mortality, stroke, CHD, CHF, systolic BP and diastolic BP	
15	**SHEP-P [213]** **Low dose Thiazide**	explanatory	Total mortality 1.11 (0.51-2.46)	Unclear	Chlorthalidone 25-50 mg daily (87%) Step II randomised to hydralazine, reserpine or metoprolol (13%).	Mortality, CHD, stroke, CHF, systolic BP and diastolic BP	

16	**SYST-EUR [214]** **Calcium Channel Blockers**	Pragmatic	Total mortality 0.86 (0.68-1.09)	Low risk	Nitrendipine, 10 mg daily, 10 mg BID, 20 mg BID, enalapril 5mg, 10 mg, 20 mg daily in evening, HCTZ 12.5 mg, 25 mg daily in morning. Matched placebos	mortality, stroke, CHD, CHF, systolic BP and diastolic BP.	
17	**TEST [173]** **Beta blockers**	Pragmatic	Total mortality 0.80 (0.56 - 1.12)	Unclear	Atenolol 50 mg daily Identical placebo tablet	Mortality, stroke, CHD, hospitalizations, BP	
18	**UKPDS 39[215]** **Beta blocker** **ACE Inhibitors**	Explanatory	Total mortality 0.77 (0.57-1.05) **0.88 (0.67-1.16)**	Unclear	Tight BP control group (Captopril 25mg -50mg b.i.d. or atenolol 50mg o.d. to 100 mg/day.	mortality, stroke, CHD and CHF, systolic BP and diastolic BP	
19	**USPHSHCSG [216]** **High dose thiazide**	explanatory	Total mortality 0.51 (0.09-2.74)	High	Chlorothiazide 500 mg BID plus rauwolfia serpentina 100 mg	Mortality, CHD, stroke, CHF, systolic BP and diastolic BP	

					BID versus placebo		
20	**VA-1[217]** **High dose thiazide**	explanatory	Total mortality 0.11 (0.01 – 1.94)	Low risk	step 1. HCTZ 100 mg plus reserpine 0.2 mg plus hydralazine 75 mg. step 2 hydralazine 150 mg.	Mortality, stroke, CHD, CHF, and diastolic BP	
21	**VA-11 [218]** **High dose thiazide**	explanatory	Total mortality 0.50 (0.24 – 1.03)	Unclear	step 1. HCTZ 100 mg plus reserpine 0.2 mg. step 2. hydralazine 75-150 mg	Mortality, CHD, stroke, CHF, systolic BP and diastolic BP	
22	**VA-NHLBI[219]** **High dose thiazide**	explanatory	Total mortality 4.96 (0.24 – 103.07)	Low risk	CHTD 50 mg, 100 mg, (53% CHTD alone) Reserpine 0.25 mg	Mortality, stroke, CHD, CHF, and diastolic BP	
23	**Wolff [175]** **High dose thiazide**	pragmatic	Total mortality 1.87 (0.36 – 9.67)	Low risk	reserpine 0.25 mg TID, chlorthiazide 0.5 g BID, or HCTZ 25 mg QID plus guanethidine if needed	Mortality, stroke, MI, CHF, systolic BP and diastolic BP	

Chapter 9: APT: Applying PRECIS-2 to Primary Care Trials Pilot and two Case studies

Figure 9.1 questionnaire for trial teams using PRECIS-2 to discuss trial design (Designed by GF with suggestions from APT Study Steering group)

APT Study: Feedback Questionnaire

Thank you for taking part in the APT study. We hope you enjoyed the session and found the tool, PRECIS-2, useful. Please could you complete the following feedback questionnaire.

Name of trial:	
Role in trial team:	

1. **The online training material contained sufficient information about PRECIS-2**

Strongly Agree		Neither agree or disagree		Strongly disagree
5	4	3	2	1

2. **The online information on how to use the tool is clear and concise**

Strongly Agree		Neither agree or disagree		Strongly disagree
5	4	3	2	1

3. **The online tool is easy to use**

Strongly Agree		Neither agree or disagree		Strongly disagree
5	4	3	2	1

4. **PRECIS-2 would have been useful to use in the design stage of the trial**

Strongly Agree		Neither agree or disagree		Strongly disagree
5	4	3	2	1

5. **Meeting to discuss independent scores lead to more accurate scores being produced than were produced independently**

Strongly Agree		Neither agree or disagree		Strongly disagree
5	4	3	2	1

6. **PRECIS-2 highlights areas of trial design which are important for your trial to achieve its goals, be that informing clinical decision making or increasing knowledge of how an intervention works.**

Strongly Agree		Neither agree or disagree		Strongly disagree
5	4	3	2	1

7. **How important do you think each of the PRECIS-2 domains is in ensuring the results from your trial are relevant to their intended audience**

i. Eligibility - Who is selected to participate in the trial?

Very Important				Not at all Important
5	4	3	2	1

ii. Recruitment - How are participants recruited into the trial?

Very Important				Not at all Important
5	4	3	2	1

iii. Setting - Where is the trial being done?

Very Important				Not at all Important
5	4	3	2	1

iv. Organisation – What expertise and resources are needed to deliver the intervention?

Very Important				Not at all Important
5	4	3	2	1

v. Flexibility - How should the intervention be delivered?

Very				Not at all

Important				Important
5	4	3	2	1

vi. Flexibility - What measures are in place to make sure participants adhere to the intervention?

Very Important				Not at all Important
5	4	3	2	1

vii. Follow-up - How closely are participants followed-up?

Very Important				Not at all Important
5	4	3	2	1

viii. Primary outcome -How relevant is it to participants?

Very Important				Not at all Important
5	4	3	2	1

ix. Primary analysis - To what extent are all data included?

Very Important				Not at all Important
5	4	3	2	1

Additional comments for the APT study team