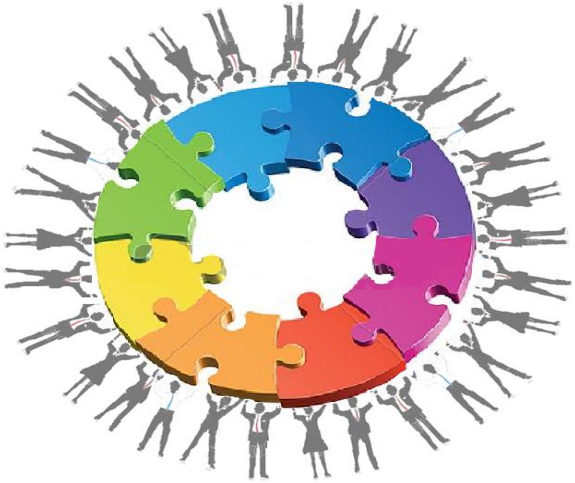


Ethics of TwiCs (Trials within Cohorts): 2nd International Symposium

7-8th November, London, UK

The University Of Sheffield.

Supported by wellcome trust

CLAHRC Yorkshire and Humber

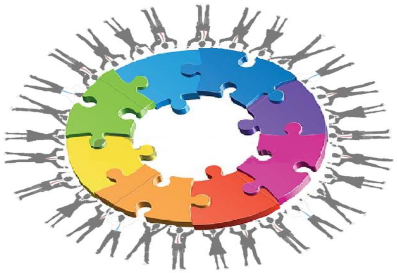
Funded & supported by NHS National Institute for Health Research

Trials within Cohorts

- Large observational cohort of people with condition of interest
- Regular measurement of outcomes
- Capacity for multiple trials

- For each trial
  - Identify those eligible
  - Random selection for trial intervention
  - Comparison of outcomes with those eligible but not randomly selected
  - Patient centred informed consent

TwiCs vs standard



Standard approach

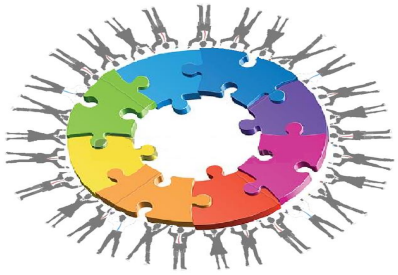
- ….. each trial recruits its own population….. Which is then disbanded
- Full information (and consent to all possibilities) up front

Trials within Cohorts (TwiCs)

- use **cohorts** (following everyone up longer term) which then ….
- ….facilitate **multiple** trials
- Information - What information is conveyed, to whom and when is tailored to the time and the person….

Consent - Yorkshire Health Study

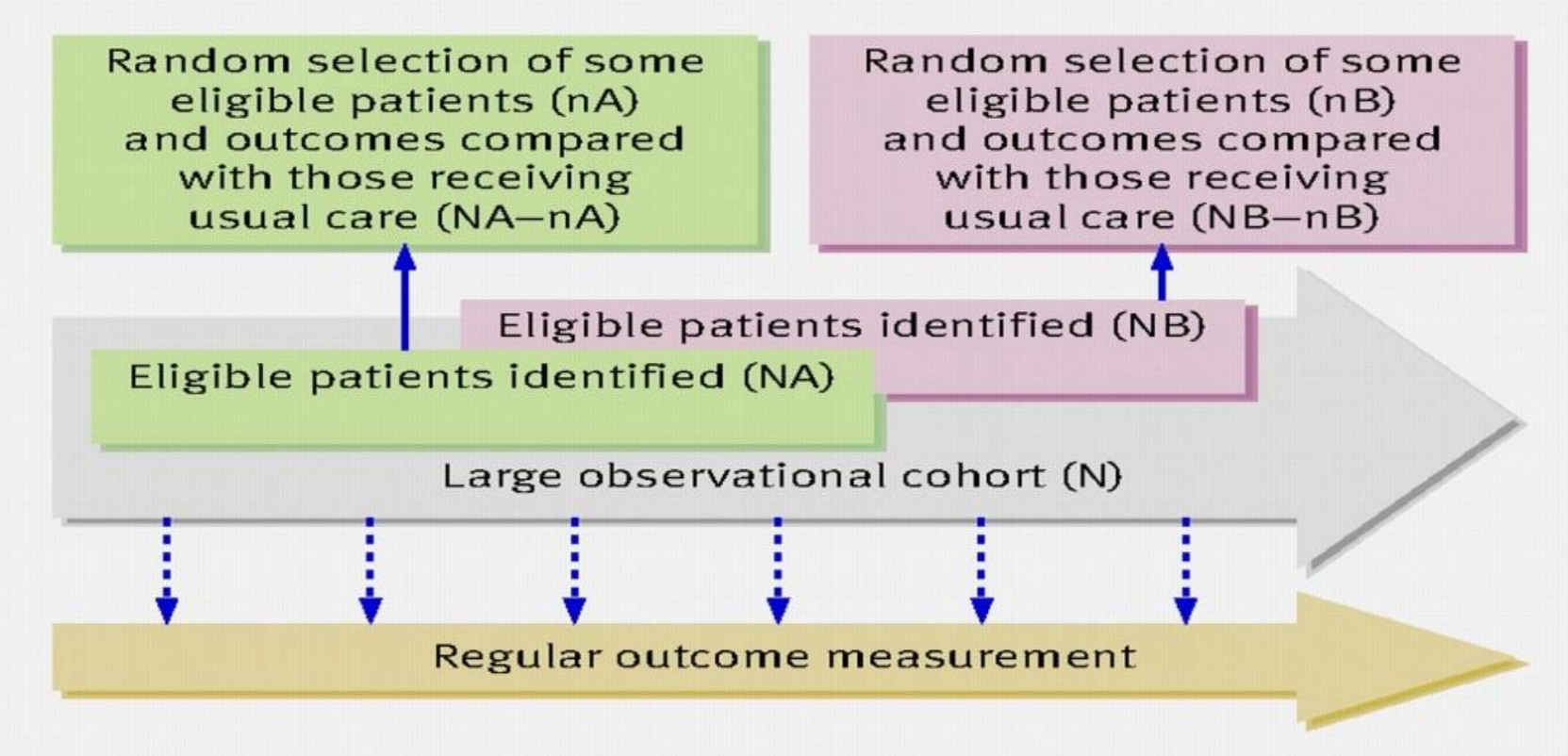
(South Yorkshire Cohort protocol. BMC Public Health 2011)



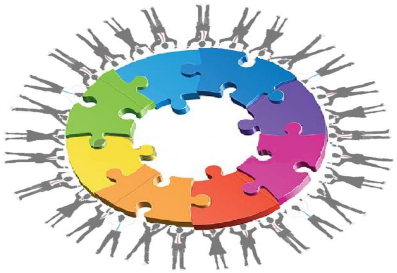
A. *Data to be used to help the NHS improve long term health*
B. *Further contact from researchers*
C. *Information provided to be used to look at the benefit of health treatments*
D. *Access to your health records*

Trials within Cohorts

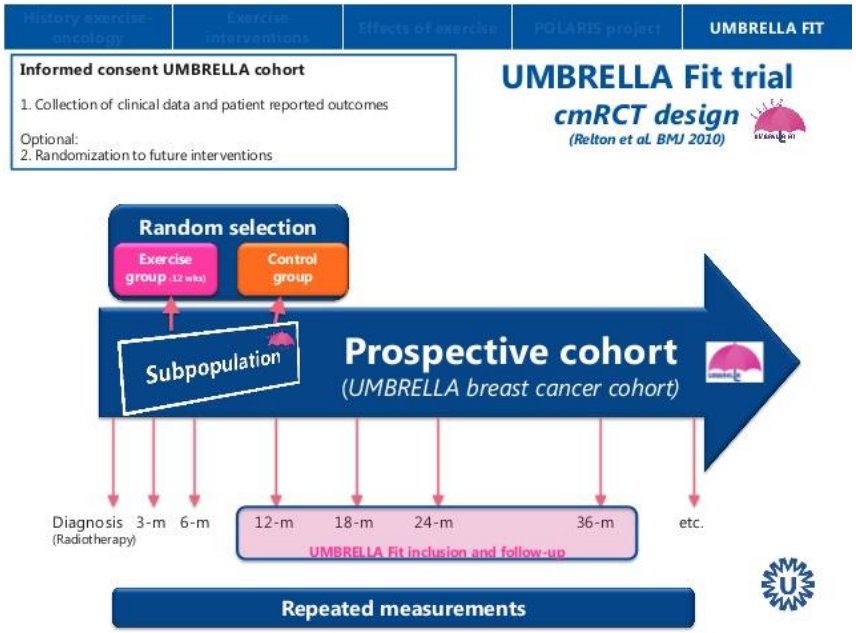
- ‘Cohort multiple RCT’ design

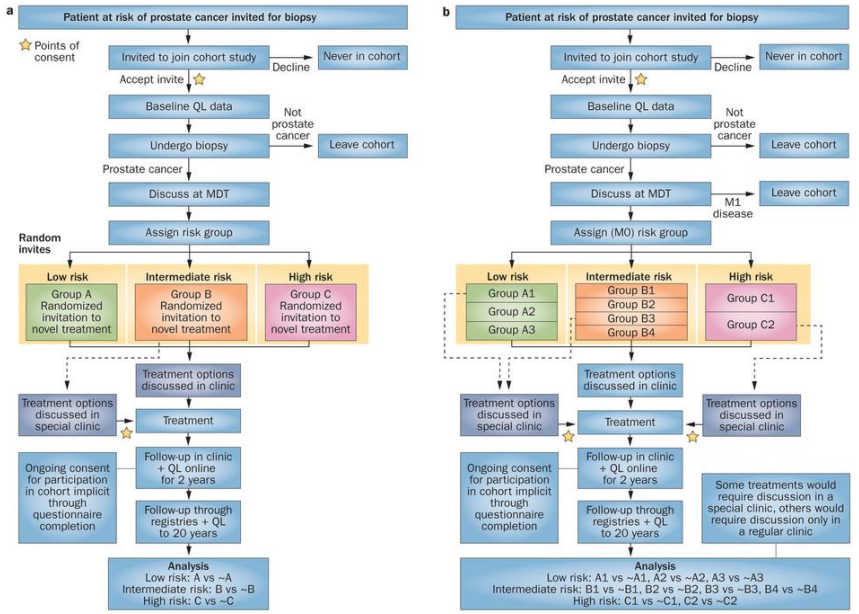


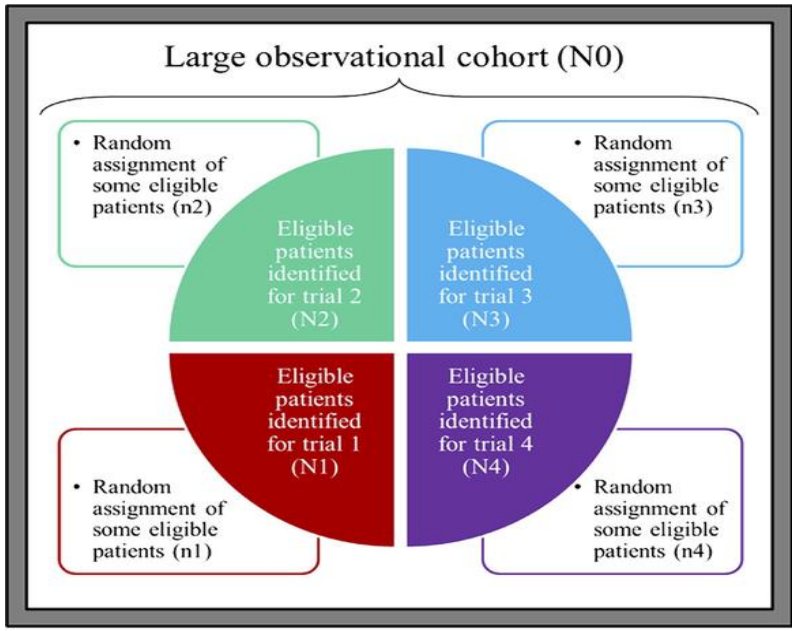
Origins

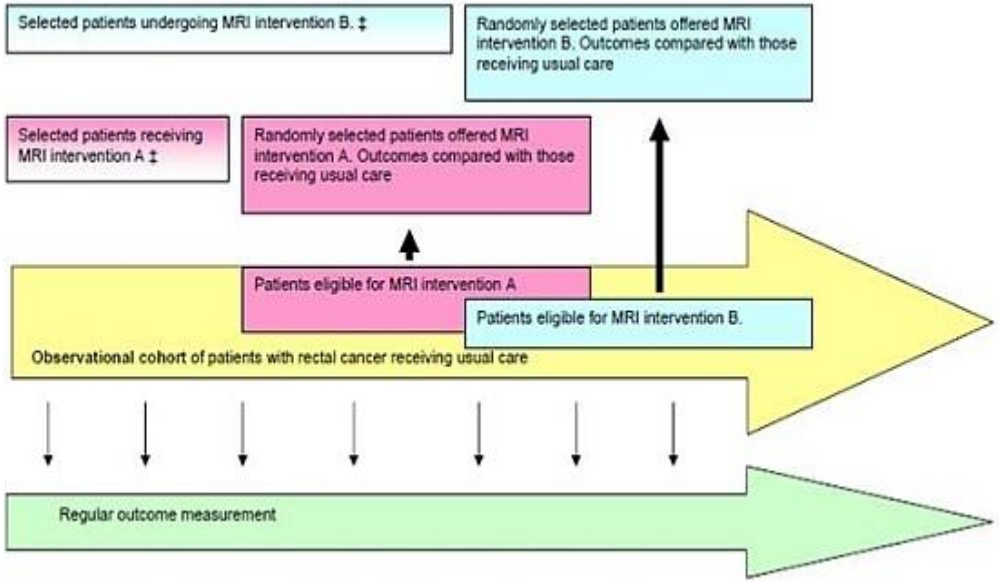


- Our prior experiences of trials
- The challenge – piloting the design - scientific review - NHS REC
- BMJ Publication
- Evolution
  - Trials within Cohorts
  - Staged consent design (Young-Afat, 2016)

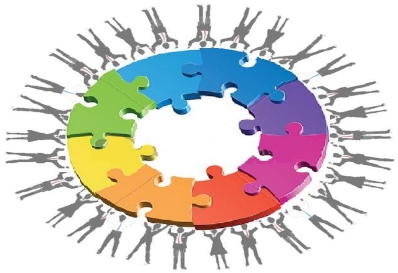

History exercise-oncology
Exercise interventions
Effects of exercise
POLARIS project
UMBRELLA FIT
Informed consent UMBRELLA cohort
1. Collection of clinical data and patient reported outcomes
Optional:
2. Randomization to future interventions
UMBRELLA Fit trial
cmRCT design
(Relton et al. BMJ 2010)
Random selection
Exercise group (12 wks)
Control group
Subpopulation
Prospective cohort
(UMBRELLA breast cancer cohort)
Diagnosis (Radiotherapy)
3-m
6-m
12-m
18-m
24-m
36-m
etc.
UMBRELLA Fit inclusion and follow-up
Repeated measurements


a
Patient at risk of prostate cancer invited for biopsy
Points of consent
Invited to join cohort study
Decline
Never in cohort
Accept invite
Baseline QL data
Not prostate cancer
Undergo biopsy
Leave cohort
Prostate cancer
Discuss at MDT
Assign risk group
Random invites
Low risk
Intermediate risk
High risk
Group A Randomized invitation to novel treatment
Group B Randomized invitation to novel treatment
Group C Randomized invitation to novel treatment
Treatment options discussed in clinic
Treatment options discussed in special clinic
Treatment
Ongoing consent for participation in cohort implicit through questionnaire completion
Follow-up in clinic + QL online for 2 years
Follow-up through registries + QL to 20 years
Analysis
Low risk: A vs ~A
Intermediate risk: B vs ~B
High risk: C vs ~C
b
Patient at risk of prostate cancer invited for biopsy
Invited to join cohort study
Decline
Never in cohort
Accept invite
Baseline QL data
Not prostate cancer
Undergo biopsy
Leave cohort
Prostate cancer
Discuss at MDT
M1 disease
Leave cohort
Assign (MO) risk group
Low risk
Intermediate risk
High risk
Group A1
Group A2
Group A3
Group B1
Group B2
Group B3
Group B4
Group C1
Group C2
Treatment options discussed in clinic
Treatment options discussed in special clinic
Treatment
Ongoing consent for participation in cohort implicit through questionnaire completion
Follow-up in clinic + QL online for 2 years
Follow-up through registries + QL to 20 years
Some treatments would require discussion in a special clinic, others would require discussion only in a regular clinic
Analysis
Low risk: A1 vs ~A1, A2 vs ~A2, A3 vs ~A3
Intermediate risk: B1 vs ~B1, B2 vs ~B2, B3 vs ~B3, B4 vs ~B4
High risk: C1 vs ~C1, C2 vs ~C2


Large observational cohort (N0)
Random assignment of some eligible patients (n2)
Random assignment of some eligible patients (n3)
Eligible patients identified for trial 2 (N2)
Eligible patients identified for trial 3 (N3)
Eligible patients identified for trial 1 (N1)
Eligible patients identified for trial 4 (N4)
Random assignment of some eligible patients (n1)
Random assignment of some eligible patients (n4)

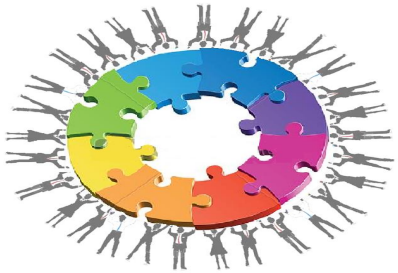

Selected patients undergoing MRI intervention B. ‡
Randomly selected patients offered MRI intervention B. Outcomes compared with those receiving usual care
Selected patients receiving MRI intervention A ‡
Randomly selected patients offered MRI intervention A. Outcomes compared with those receiving usual care
Patients eligible for MRI intervention A
Patients eligible for MRI intervention B.
Observational cohort of patients with rectal cancer receiving usual care
Regular outcome measurement

TwiCs: how is it being used?



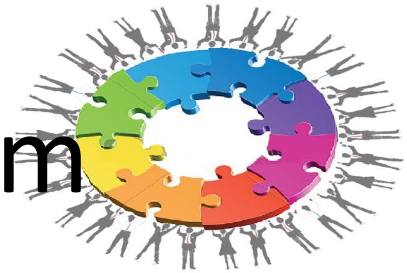
- Countries: Australia, Canada, Finland, France, Netherlands, UK, USA
- Various settings: Hospital & non hospital
- Cohort populations: ADHD, Cancer, Depression, Early Life, Hep C, HIV, Hip fracture, IBS, Falls in the elderly, people with LTC, older people, Severe Mental Illness, rare diseases (scleroderma), Young indigenous
- Interventions being trialled: acupuncture, CBT skills based training, compression vests, exercise programmes, fracture treatments, homeopathy, supportive listening, chemo – radiation/ irradiation, manual therapies, models of care, nutritional therapy, podiatry, psychological treatments, screening, surgery
- Funders: Charity (Big Lottery, Condition based), CIHR, NIHR,

1st TwiCs symposium



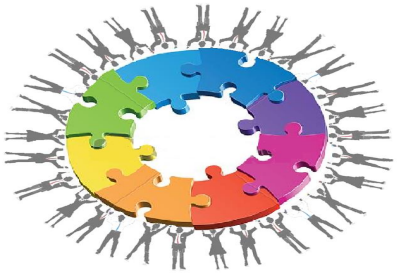
- “ yes, ….. But is it ethical?”

Purpose 2nd TwiCs symposium



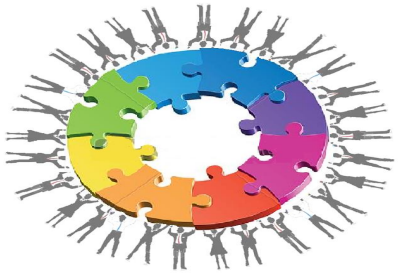
- Forum to discuss ethical questions
- Share perspectives on the design
- Discuss how TwiCs relate to current ethical framework
- Identify future directions for conceptual and empirical research

Day one:
Identifying questions, learning from experience



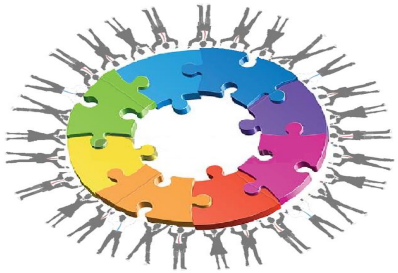
Welcome and introduction **CHAIR: Professor Jon Nicholl, University of Sheffield, UK**	
What is the TwiCs design, and how is it being used?	Dr Clare Relton, ScHARR University of Sheffield, UK
How do TwiCs trials fit into Pragmatic/Explanatory trials framework?	Professor Merrick Zwarenstein, Western University, Canada
Tea and coffee	
KEY NOTE TALK Randomisation without consent in RCTs – review of use (and terminology discussion)	Professor James Flory Weill Cornell Medical College, USA
FORBOW: Experience from a prevention trial within a cohort of youth at high risk of severe mental illness	Dr Rudolf Uher Dalhousie University, Canada
UMBRELLA FIT: Experience from a trial within a hospital based breast cancer cohort	Professor Anne May, UMC Utrecht, Netherlands
Lunch break and poster session 1	

Day one:
Identifying questions, learning from experience



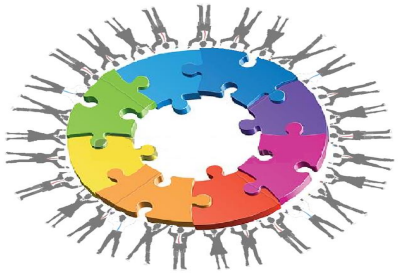
CHAIR: Professor James Flory, Weill Cornell Medical College, USA	
KEY NOTE TALK Ethical Issues in TwiCs and other Pragmatic Trial Designs: An Overview	Professor Scott Y Kim Dept of Bioethics, National institutes of Health (NIH), USA
KEYNOTE TALK The ethics of inefficiency	Professor Shaun Treweek University of Aberdeen, UK
Tea and coffee	
TwiCS and big data: opportunities and challenges	Professor Tjeerd Van Staa University of Manchester, UK
Patient-reported outcomes in routine care: impact for TwiCs	Dr Andrew Vickers Memorial Sloan Kettering Cancer Centre, USA
PANEL DISCUSSION Where do we go from here?	

Day two:
……Going forward



Welcome, introduction and recap Chair – Professor Helena Verkooijen, Utrecht Medical Centre, Netherlands	
HRA guidance policy and strategy on Informed Consent for simple and efficient trials. Randomisation without consent: survey of UK RECs	Clive Collett, Amanda Hunn UK Health Research Authority
Ethics boards and consent – introduction & sharing of experiences?	Sophie Welch Independent research consultant
KEY NOTE TALK Why and when should control groups consent? Do ethical considerations relating to harm, burden, rights and reasonable expectations help us to answer this question?	Professor Søren Holm University of Manchester, UK
Tea and coffee	
Obtaining ethics approval for the cmRCT design from 31 ethics committees in 4 countries: a challenge?	Dr Linda Kwakkenbos, McGill University, Canada
What do patients understand of the TWiCs design?	Dr Sophie Gerlich, UMC Utrecht, Netherlands
DISCUSSION	
Lunch break and poster session 2	

Day two:
……Going forward



CHAIR Professor Søren Holm	
Future directions for research Challenges for future studies in fragile patients- Joanne vd Velden, Effectiveness & acceptability of tailored disclosure? Clare Relton Evidence of distress related to informed consent? Andrew Vickers SHED Share ethical debate amongst UK RECs – Amanda Hunn	Introduced by Danny Young-Afat, UMC, Utrecht, Netherlands Discussion with mini (2- 10 min) presentations
Panel discussion and concluding remarks	

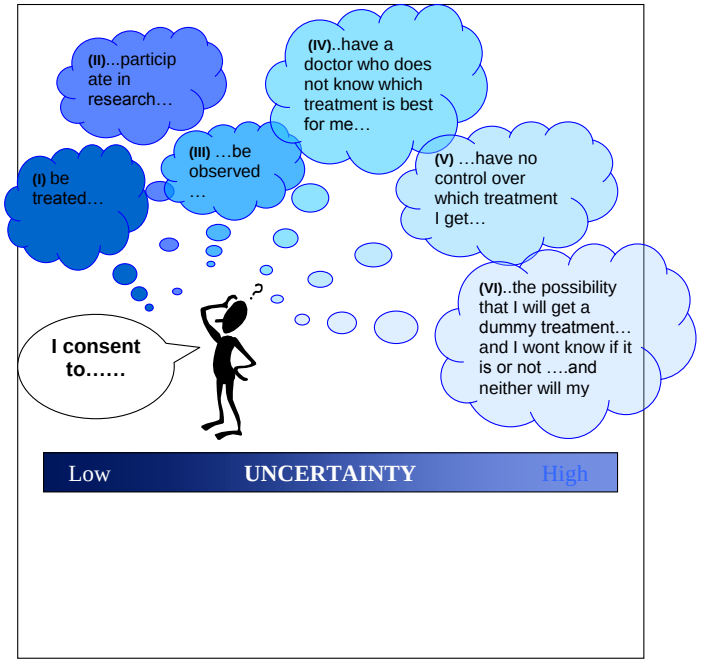
Language - design

- Pragmatic designs
- Explanatory designs
- Cohort multiple RCT design
- Cohort embedded RCT design
- Trials within Cohorts design (TwiCs)
- Staged consent RCT design
- Randomised consent design
- Zelen design (single and double)
- Randomised registry trials
- Comprehensive cohort trials
- Standard of care (SOC)
- Treatment as usual (TAU)

Language - IC

- Informed consent
- Fully informed consent
- Patient-centred consent
- Tailored disclosure
- Proportionate consent
- Randomisation without consent (RWOC)
- Broad consent
- Pre randomisation broad consent

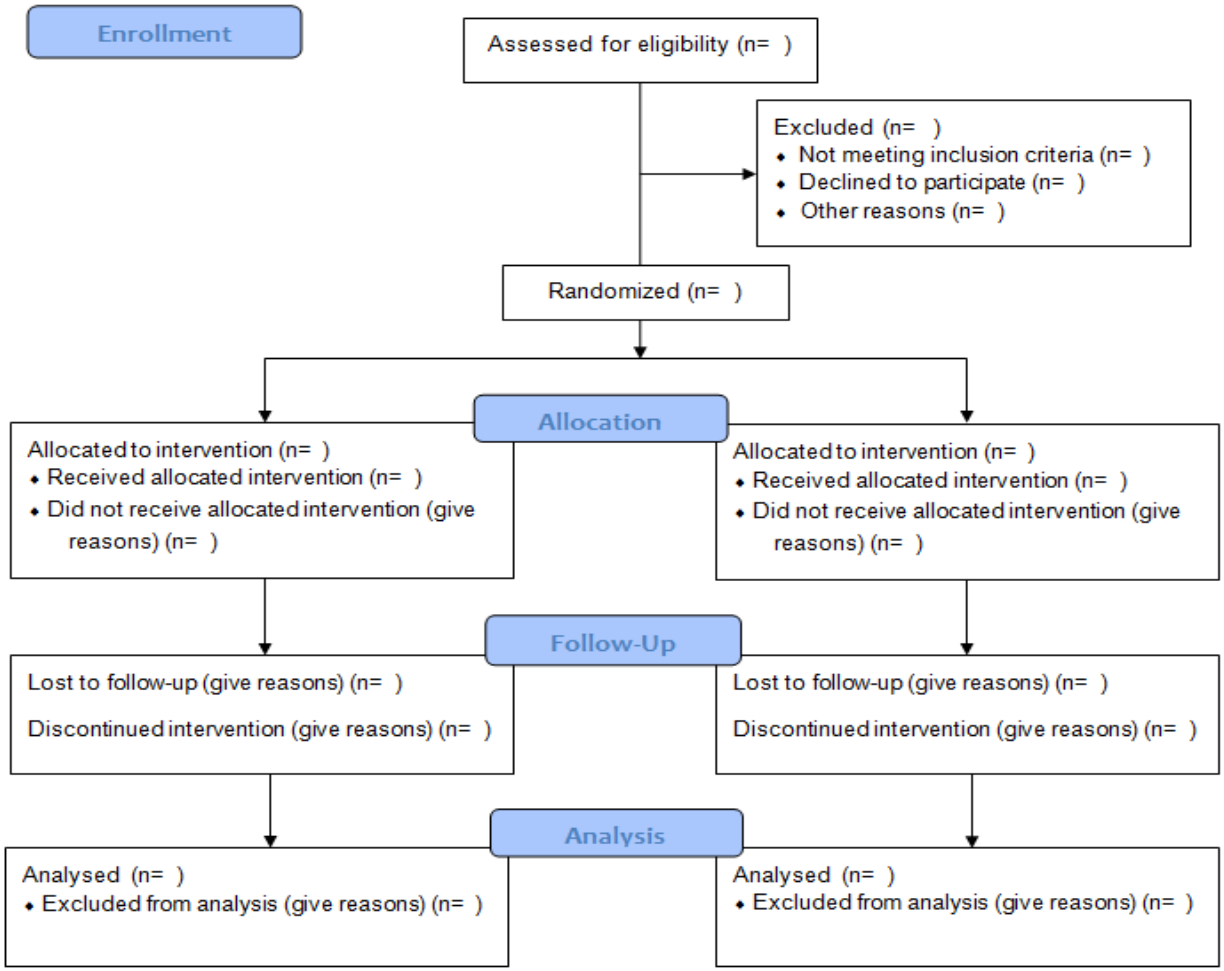
Consent to?

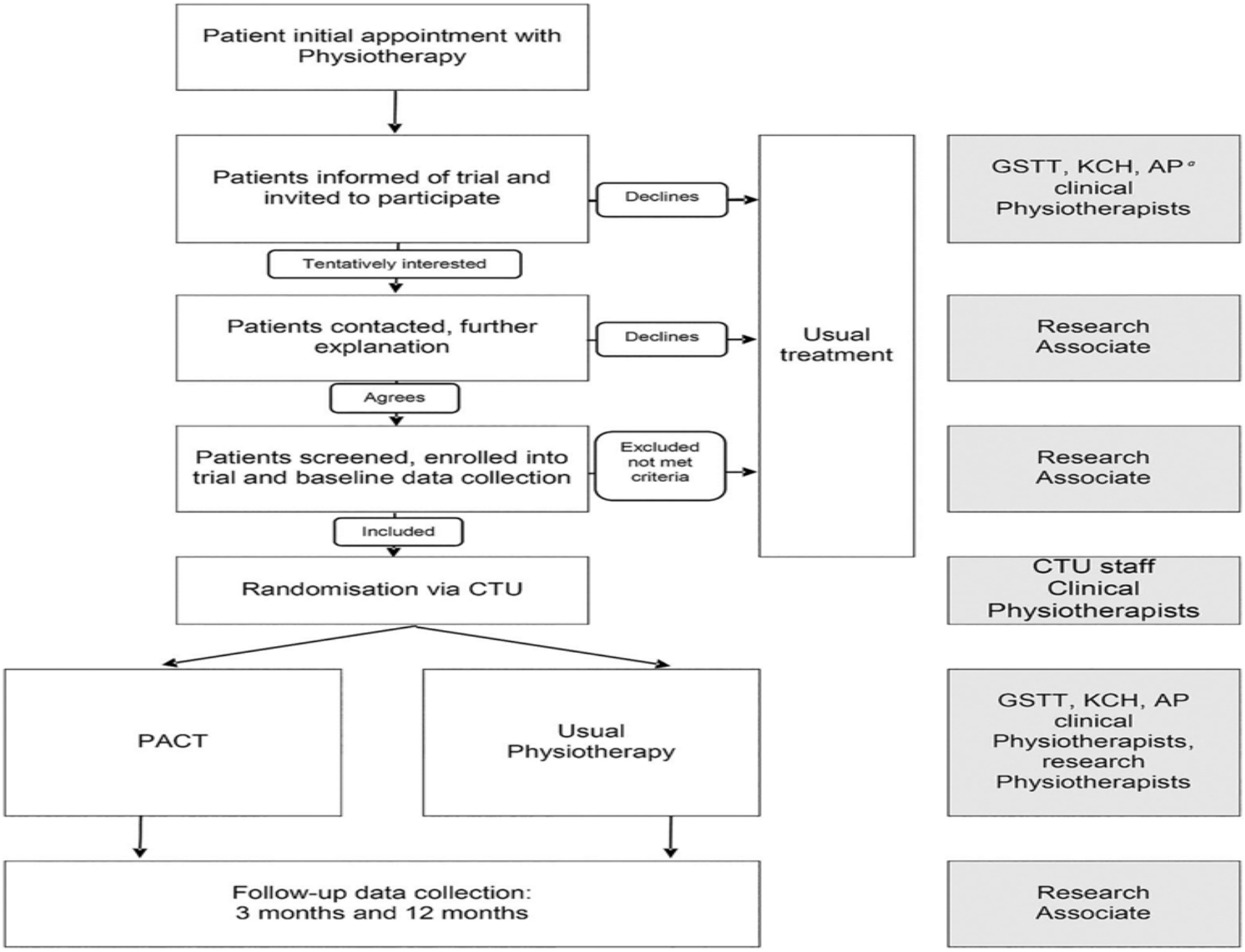


- To provide/have data used
- To have data linked
- For data to be used in an (intervention?) study
- To be contacted again
- To be randomised
- To be offered tx
- To receive tx

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram




Patient initial appointment with Physiotherapy
Patients informed of trial and invited to participate
Declines
Tentatively interested
Patients contacted, further explanation
Declines
Agrees
Patients screened, enrolled into trial and baseline data collection
Excluded not met criteria
Included
Randomisation via CTU
Usual treatment
PACT
Usual Physiotherapy
Follow-up data collection: 3 months and 12 months
GSTT, KCH, AP clinical Physiotherapists
Research Associate
Research Associate
CTU staff Clinical Physiotherapists
GSTT, KCH, AP clinical Physiotherapists, research Physiotherapists
Research Associate