research activities, there is a risk that research that would not be ethically permissible in the European Union is exported to countries where the legal and regulatory framework for research is not as stringent [3]. The Trials within Cohorts (TwiCs) study design offers the real world applicability of results that is desperately needed in LMICs. However, for the TwiCs design to be of value in LMICs there must be care to avoid ethics dumping with sensitivity to local preferences, needs and environment.

Method

A broad based consultative exercise was undertaken to identify and analyse vulnerabilities for exploitation (ethics dumping) in research in LMICs. Data was garnered from multi-level ethics bodies, policy advisors/makers, civil society organisations, funding organisations, industry and academic scholars, more than 30 members of ethics committees in LMICs, representatives from vulnerable populations in LMICs and an open call for case studies of ethics dumping in LMICs.

Results

A wide variety of vulnerabilities were identified and analysed thematically. For example, those who live in poor circumstances are more vulnerable to undue inducement and those who lack education may struggle to understand the research information. Cultural differences can influence the interpretation of certain ethical principles and a lack of resources and infrastructures can seriously affect the validity of the research. Additionally, many studies lack relevance for the communities in which they are undertaken and offer no potential for benefit from the results; this can leave the participants with a sense of being used or abused.

Conclusion

The logistical and ethical challenges for the conduct of any cohort studies in LMICs are significant. Community engagement and local ownership are essential for sustainability and the research may require significant investment in the local community. The TwiCs design offers a means of ensuring that studies are relevant to specific communities and as such, may be of great value in LMICs.

Acknowledgements

This investigation has arisen from a European Union's Horizon 2020 project entitled *TRUST* (grant agreement No 664771). Thank you to members of the TRUST consortium for their input.

References

1. Viergever RF. The mismatch between the health research and development (R&D) that is needed and the R&D that is undertaken: an overview of the problem, the causes, and solutions. Global health action. 2013;6.
2. Evans JA, Shim J-M, Ioannidis JP. Attention to local health burden and the global disparity of health research. PLoS One. 2014;9(4):e90147.
3. Commission E. Horizon 2020, the EU framework programme for research and innovation: Ethics 2016 [Available from: https://ec.europa.eu/programmes/horizon2020/en

Topic 3: Examples

A10

Experience from a prevention trial within a cohort of youth at high risk of severe mental illness

Rudolf Uher (uher@dal.ca)
Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, B3H 2E2, Canada
Trials 2017, **18(Suppl 2):**A10

Severe mental illness includes schizophrenia, bipolar disorder and the most severe cases of depression. The Families Overcoming Risks and Building Opportunities for Well-being (FORBOW) program aims to find out how we can effectively prevent severe mental illness through early indicated interventions. The Trial within Cohorts (TwiCs) design makes it possible to test the long term effect of interventions with strong external validity.

FORBOW enrols children and youth (age 1-21 years) in an accelerated cohort with annual assessments of cognitive development and psychopathology [1]. Youth participants are recruited through their parents, with an oversampling of parents who are receiving health services for severe mental illness, irrespective of whether any psychopathology is present in the youth. To date, we have enrolled 317 participants in the cohort and we have been able to follow-up 95% of cohort participants annually. The combination of family history of severe mental illness and early antecedents including affective lability, anxiety, psychotic symptoms and basic symptoms allows efficient early identification of risk.

Embedded within the cohort is a trial of Skills for Wellness (SWELL), a psychological early intervention which coaches children and adolescents in coping and emotional skills needed to develop resilient mental health. Eligible participants who are 9-21 years old and present with one or more antecedents are randomly allocated to be offered the SWELL intervention or not in a 1:1 ratio. The participants are not actively seeking treatment at the time of allocation. To date, 36 participants have been randomly allocated and the intervention participation rate has been 83% with positive feedback from participating families. This contrasts with experiences from another early intervention trial in a non-help seeking population that had similar aims but followed traditional clinical trial design and was stopped because of failure to enrol participants [2,3]. The early experience suggests that the TwiCs design enables externally valid tests of preventive interventions with long-term follow up.

Trial registration:

ClinicalTrials.gov Identifier: NCT01980147

References

1. Uher R, Cumby J, MacKenzie LE, Morash-Conway J, Glover JM, Aylott A, Propper L, Abidi S, Bagnell A, Pavlova B, Hajek T, Lovas D, Pajer K, Gardner W, Levy A, Alda M: A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. BMC Psychiatry 2014; 14344
2. Nauta MH, Festen H, Reichart CG, Nolen WA, Stant AD, Bockting CL, van der Wee NJ, Beekman A, Doreleijers TA, Hartman CA, de Jong PJ, de Vries SO: Preventing mood and anxiety disorders in youth: a multicentre RCT in the high risk offspring of depressed and anxious patients. BMC Psychiatry 2012; 1231
3. Festen H, Schipper K, de Vries SO, Reichart CG, Abma TA, Nauta MH: Parents' perceptions on offspring risk and prevention of anxiety and depression: a qualitative study. BMC Psychol 2014; 2:17

A11

Experience from an exercise cohort multiple TwiCs Controlled Trial (cmRCT) within a hospital based breast cancer cohort: UMBRELLA FIT study

Anne M May[1], Roxanne Gal[1], Evelyn M Monninkhof[1], Danny A. Young Afat[1,2], Carla H van Gils[1], Rolf HH Groenwold[1], Helena M Verkooijen[2]
[1]Department of Clinical Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Imaging Division, University Medical Center Utrecht, Utrecht, The Netherlands
Correspondence: Anne M May (a.m.may@umcutrecht.nl)
Trials 2017, **18(Suppl 2):**A11

Introduction

Exercise interventions show beneficial effects on cancer patients' quality of life. However, effect sizes are often small, which might be partly explained by contamination; i.e., patients randomised to the control arm adopt the exercise intervention. Also, patients may refrain from participation, or drop-out after being randomised to the control arm. Applying a cohort multiple RCT (cmRCT) design might overcome the disadvantages of conventional RCTs when blinding of the intervention is impossible. UMBRELLA FIT studies the feasibility of cmRCT in exercise-oncology research. Effects of the intervention on quality of life will be investigated.

Methods

The 'Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation (UMBRELLA cohort)' started in 2013 in the UMC Utrecht (The Netherlands). Currently >1600 breast cancer patients participate. Over 85% provided broad consent to be randomly

selected for future experimental interventions or to serve as control without further notice. For the UMBRELLA FIT study, 168 physically inactive breast cancer patients (12-18 months post-baseline), who gave broad consent are randomised to a 12-week supervised exercise intervention or control. Endpoints are contamination, participation, generalizability and retention (methodological) and quality of life (effectiveness). In addition, instrumental variable analysis will be performed taking drop-out/non-compliance after randomisation into account.

Results

The UMBRELLA FIT trial recruitment started in October 2015, since then 130 patients have been randomised. Of 65 intervention patients, 55% agreed to participate. Reasons for non-participation were mainly time constraints, dislike of exercise, or avoidance of confrontation with their disease. Acceptance rate of the intervention has been lowest in the summer period.

Conclusion

It is anticipated that recruitment will be completed in 2017. Results on feasibility and effectiveness will be reported.

Trial registration

The Netherlands National Trial Register NL.52062.041.15 / NTR5482

Acknowledgements

The abstract is presented on behalf of the UMBRELLA study group. We thank the study team of the UMBRELLA cohort at the department of Radiotherapy, Imaging Division and Julius Center of the University Medical Center Utrecht (UMCU) for running the cohort and collecting the data. This work was supported by a Veni grant from the The Netherlands Organisation for Health Research and Development (ZonMw 016.156.050). In addition, funding was provided by the department of Radiotherapy, Imaging Division of the University Medical Center Utrecht (UMCU), and the department of Clinical Epidemiology, Julius Center for Health Sciences and Primary Care, UMCU.

A12

Patient-reported outcomes in routine care: impact for TwiCs

Andrew Vickers (vickersa@mskcc.org)
Memorial Sloan Kettering Cancer Centre, New York, NY, USA
Trials 2017, **18(Suppl 2):**A12

Clinicians routinely collect information on patient-reported outcomes as a part of clinical care. For instance, a rheumatologist will want to understand a patient's level of pain and functioning in order to consider the effectiveness of a new treatment; a cancer surgeon will want to know how a patient is recovering from surgery in order to determine whether persistent symptoms require attention. There are numerous reasons why the use of standardized questionnaires for such purposes is far superior to informal discussion.

At Memorial Sloan Kettering Cancer Centre (MSKCC) we have pioneered the use of electronic methods to gather patient-reported outcomes as part of standard care. Current clinical projects include urinary and erectile function after radical prostatectomy; pain and recovery after gynaecological surgery; bowel, urinary and sexual function after rectal surgery; patient satisfaction with breast reconstruction; gerontology; pain and discomfort during prostate biopsy. We ensure that clinical staff are involved in the development of the questionnaire, the design of the report given to clinicians summarising patient responses and its integration into clinical workflow. By optimizing the clinical value of patient-reported outcomes we ensure that patients do indeed complete them in routine practice.

Data obtained to aid the clinical consultation can then be reused as the endpoints of randomised trials, facilitating the sort of clinically-integrated research associated with many TwiCs approaches. For instance, we are currently conducting a traditional randomized trial comparing two approaches to port-site closure after minimally-invasive surgery, using patient-reported hernia as an endpoint. The critical point is that all of our patients are asked to provide data on hernia, whether or not they take part in the trial. Hence, although our trial is not in a TwiCs context, it demonstrates how use of routinely collected patient-reported outcomes can facilitate the sort of low-cost, pragmatic trials common in TwiCs.

A13

Obtaining ethics approval for the cmRCT design from 39 ethics committees in 5 countries: the Scleroderma Patient-centered Intervention Network (SPIN)

Linda Kwakkenbos[1,2,3], Marie-Eve Carrier[2], Brett D Thombs[1,2], and the SPIN investigators
[1]Department of Psychiatry, McGill University, Montréal, Québec, Canada; [2]Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, Québec, Canada; [3]Behavioural Science Institute, Clinical Psychology, Radboud University, Nijmegen, the Netherlands
Correspondence: Linda Kwakkenbos (kwakkenbosl@gmail.com)
Trials 2017, **18(Suppl 2):**A13

Background

People with rare diseases do not typically have access to evidence-based self-management and psychosocial interventions, and conducting rigorous, adequately powered trials is difficult. The Scleroderma Patient-centered Intervention Network (SPIN) is a collaboration of scleroderma centers, clinicians, patient organizations and investigators from Canada, the US, Mexico and Europe, whose aim is to develop, test, and disseminate self-management and psychosocial interventions for people living with the rare disease scleroderma [1].

Methods

SPIN utilizes the cohort multiple RCT (cmRCT) design to collect longitudinal data on patient-reported outcomes in scleroderma via the Internet and to test online interventions on an ongoing basis. SPIN is in the process of enrolling 2,000 scleroderma patients for an ongoing web-based cohort dedicated to better understand problems important to scleroderma patients, validating outcome measures, and informing development of interventions. SPIN will also use the cohort framework to develop, evaluate, and deliver the online support tools. Eligible participants are at least 18 years of age, have a scleroderma diagnosis, speak one of the SPIN languages (currently English, French or Spanish) and have access to the Internet. Upon enrolment in the Cohort, participants allow their physician to provide their contact information and basic medical information to the SPIN team. Once participant's medical data are entered online, they receive emails at 3-month intervals that invite them to complete online assessments. The cmRCT design allows us to recruit very large samples for trials, even in a rare disease context, and reduces the cost of re-starting the recruitment process each time, including getting new ethics approval for each participating center.

Results

Since enrolment started in April 2014, SPIN has recruited over 1,500 scleroderma patients from 39 centers in Canada, the US, the UK, France and Mexico after obtaining approval from the local ethics board for each center. SPIN was recently funded to evaluate the effectiveness of an online hand exercise program and a scleroderma disease self-management program in two pragmatic RCTs embedded in the SPIN Cohort, including 400-500 patients in each. For these trials that SPIN will run through the Cohort, ethics approval is only required from the SPIN coordinating center at the Jewish General Hospital of McGill University, which adds to the feasibility of conducting multiple trials.

Discussion

The use of the cmRCT design and development of self-guided eHealth interventions allows SPIN to develop, rigorously test, and deliver interventions for people with a rare disease from around the world.

Acknowledgements

SPIN has been funded by grants from the Canadian Institutes of Health Research (TR3-119192, PJT-148504, PJT-149073) and the Arthritis Society. In addition, SPIN has received institutional contributions from the Lady Davis Institute for Medical Research of the Jewish General Hospital, Montréal, Canada and from McGill University, Montréal, Canada. SPIN has also received support from the Scleroderma Society of Ontario, the Scleroderma Society of Canada, and Sclérodermie Québec. Dr. Kwakkenbos was supported by a CIHR Banting Postdoctoral Fellowship. Dr. Thombs is supported by an Investigator Award from the Arthritis Society.