Using the Cohort Multiple Randomized Controlled Trial (cmRCT) Design for Pragmatic Trials in a Rare Disease Context:

The Scleroderma Patient-centered Intervention Network (SPIN)

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What is Scleroderma (Systemic Sclerosis)

• The word **scleroderma** comes from the greek "scleros" meaning hard and "derma" meaning skin
• SSc results in autoimmune changes, fibrosis (scarring) and severe vascular problems (reduced bloodflow to organs and extremities)
Trials of Psychosocial and Rehabilitation Interventions in Rare Diseases

• Search for studies across all 6,632 rare diseases listed on NIH Office of Rare Disease Research (July 2011)

• Sought randomized controlled trials (RCT) of psychosocial and rehabilitation interventions with at least 100 patients

• Found only 1 RCT (an exercise intervention for patients recovering from SARS)
Treatment of scleroderma

EULAR guidelines (Kowal-Bielecka et al. 2009):

“There are also other treatment options for the management of SSc patients, such as physiotherapy, education, new experimental therapies, etc, which were beyond the scope of this project or could not be included because of the lack of expert consensus”
SPIN: The Scleroderma Patient-centered Intervention Network
Challenges

• To develop supportive interventions (psychosocial, rehabilitation) that are:
  • Accessible to people with scleroderma
  • Low cost for feasible delivery
  • Can be disseminated on an ongoing basis post-trial

• To conduct high-quality trials to confidentially assess effect of interventions (including at least 200-300 people)
SPIN – Key components

1) Patient organization partnerships throughout the research process and as end user
2) International network of clinical research centers
3) Virtually delivered interventions
4) Cohort multiple RCT (cmRCT) design in rare disease context
Partnering with Scleroderma Patient Organizations
SPIN – Key components

1) Patient organization partnerships throughout the research process and as end user
2) **International network of clinical research centers around the world**
3) Virtually delivered interventions
4) **Cohort multiple RCT (cmRCT) design in rare disease context**
SPIN Recruiting Sites

- English and French
  - Canada (14 sites)
  - USA (11 sites)
  - UK (2 sites)
  - France (Paris center + national network)
  - Australia (2 sites)

- Other – Translations in Progress
  - The Netherlands (2 sites)
  - Mexico (1 site)
  - Span (1 site)
SPIN – Key components

1) Patient organization partnerships throughout the research process and as end user
2) International network of clinical research centers around the world
3) **Virtually delivered interventions**
4) Cohort multiple RCT (cmRCT) design in rare disease context
Online self-help interventions

- Increasingly common, for instance:
  - Self-management in diabetes (e.g., Lorig et al, 2010)
  - Depressive symptoms (e.g., Gellatly et al, 2007)
  - Anxiety (e.g., Hirai & Clum, 2006)

- Self-guided online interventions were effective in reducing elevated levels of depressive symptoms (Cuijpers et al, 2011)
  - 7 trials (total N = 1,362)
  - d=0.28 (p<0.001)
SPIN – Key components

1) Patient organization partnerships throughout the research process and as end user
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4) Cohort multiple RCT (cmRCT) design in rare disease context
cmRCT versus Standard Parallel Arms RCT

- Cohort
- Multiple

Pre-randomization Consent
cmRCT design: Cohort
The SPIN Cohort

Large international study with people with scleroderma (N=2,000+):

- Online questionnaires every 3 months
- Information on problems important to patients
- How best to measure these outcomes
- Natural history of scleroderma and treatment as usual
Ethics: Cohort consent

Consent elements **for inclusion in cohort:**

1) To provide observational data that will be used to better understand problems that may be important to people with scleroderma

2) To use responses to determine if someone is eligible for an intervention, and to be contacted to participate in interventions

3) To compare responses to the responses of people in the cohort who participated in an intervention (in which patient did not participate)
Ethics: Cohort consent

What we learned (21 sites ethics approved to date):

1) Some sites will remove 3 key cmRCT components, so need to describe rationale and review all site-specific ethics protocols and informed consent documents.

2) No ethical concern about trial design so far.

3) Standard rogue ethics board rules apply.
Internet-based Data Collection

1) Sites provide basic medical data and trigger email to patients to activate their accounts

2) Once activated, 1 month to complete baseline data, then emails to complete data every 3 months

3) Measures include (1) core measures for each trial currently being built; (2) general disability and function; (3) currently, measures on body image and social anxiety for validation.

4) Complex data management to handle cohort and trials with eligibility and trial-specific measures.
Data Collection: Update

1) Initiated with two sites in April with most going online this fall. Over 400 patients enroled, though 20-30% non-activated.

2) Activation issues:
   1) Email reminders to patients (every week after enrolment)
   2) Email reminder to enrolling site (2 weeks after enrolment)
   3) Follow-up phone calls by us (4 weeks after enrolment)
   4) Frequently Asked Questions sheet
   5) Youtube instruction video
   6) Toll-free number
cmRCT design: Trials

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RANDOM SELECTION OF SOME ELIGIBLE PATIENTS AND OUTCOMES COMPARED WITH THOSE RECEIVING USUAL CARE
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ELIGIBLE PATIENTS IDENTIFIED (NB)
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ELIGIBLE PATIENTS IDENTIFIED (NB)
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LARGE OBSERVATIONAL COHORT (N)
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REGULAR OUTCOME MEASUREMENT
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"COHORT MULTIPLE RCT DESIGN"
RELTON ET AL. BMJ 2010
Coping with emotions & stress

Positive Coping with Health Conditions
A Self-Care Workbook
Scleroderma Self-Management

Internet-enhanced management of fibromyalgia: A randomized controlled trial

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ABSTRACT

Both pharmacological and non-pharmacological interventions have demonstrated efficacy in the management of fibromyalgia (FM). Non-pharmacological interventions however are far less likely to be used in clinical settings, in part due to limited access. This manuscript presents the findings of a randomized controlled trial of an Internet-based exercise and behavioral self-management program for FM designed for use in the context of a routine clinical care. 118 individuals with FM were randomly assigned to either (a) standard care or (b) standard care plus access to a Web-Enhanced Behavioral Self-Management program (WEB-SM) grounded in cognitive and behavioral pain management principles. Individuals were assessed at baseline and again at 6 months for primary endpoints: reduction of pain and an improvement in physical functioning. Secondary outcomes included fatigue, sleep, anxiety and depressive symptoms, and a patient global impression of improvement. Individuals assigned to the WEB-SM condition reported significantly greater improvement in pain, physical functioning, and overall global improvement. Exercise and relaxation techniques were the most commonly used skills throughout the 6 month period. A no-contact, Internet-based, self-management intervention demonstrated efficacy on key outcomes for FM. While not everyone is expected to benefit from this approach, this study demonstrated that non-pharmacological interventions can be efficiently integrated into routine clinical practice with positive outcomes.

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Coping with appearance changes

Changing Faces.

Changing the way you face disfigurement
Improving Hand Function

Scleroderma hand problems:

- Stiffness in hands
  - 81% at least sometimes
  - Of these patients, 73% moderate, severe, or extreme impact on daily activities
- Difficulty making fists (67%, 73%)
- Difficulty holding objects (67%, 76%)
Trial Notes Thus Far

1) Patients receive a list of 10 interventions that SPIN may develop, but are not told of interventions being developed currently
   1) Challenge in rare disease community with active patient partners
   2) Website designed to encourage patient interest and support, but not disclose interventions underway

2) Eligibility:
   1) Threshold on core measure (e.g., symptoms of depression)
   2) Signalling questions indicating interest in doing intervention if available
   3) Pattern of cohort assessment completion
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