PALLIATIVE CARE RESEARCH COOPERATIVE

Deprescribing trials in palliative care: lessons learned from the statin deprescribing trial

US Deprescribing Research Network (USDeN)
September 14, 2021
Jean S. Kutner, MD, MSPH
Professor of Medicine, University of Colorado School of Medicine
Co-Chair, Palliative Care Research Cooperative Group

Funded by U.S. National Institute of Nursing Research, National Institutes of Health (UC4-NR012584, U24-NR014637, U2CNR014637)

Disclosures

- The University of Colorado receives grant support on behalf of Dr. Kutner from the NIH and PCORI.
- Dr. Kutner serves on the National Advisory Board for the Cambia Sojourns Scholars Program.

Outline

- Context – the PCRC
- Statin discontinuation trial – brief overview
- Lessons learned
  - Start up
    - Rebudgeting
    - IRB
    - Site and Site PI recruitment and training
    - Outcome(s) and measure selection
  - Conduct
    - Recruitment
    - Site performance
    - DSMB role/ Primary study endpoint change
    - Adverse event definition and adjudication
  - Publications – primary and secondary
  - De-identified data repository and secondary data analysis

Context - Palliative Care Research Cooperative Group (PCRC)

- Established in 2010, with foundational funding by a cooperative agreement from the National Institute of Nursing Research (NINR) (UC4NR012584), and continuation funding in 2013 and 2018 (U24NR014637 and U2C NR014637).
- A central purpose: to facilitate - through a well-functioning cooperative group - the conduct of collaborative, rigorous, multisite end-of-life and palliative care (EOLPC) research.

PCRC Vision *(revised Aug 2017)*

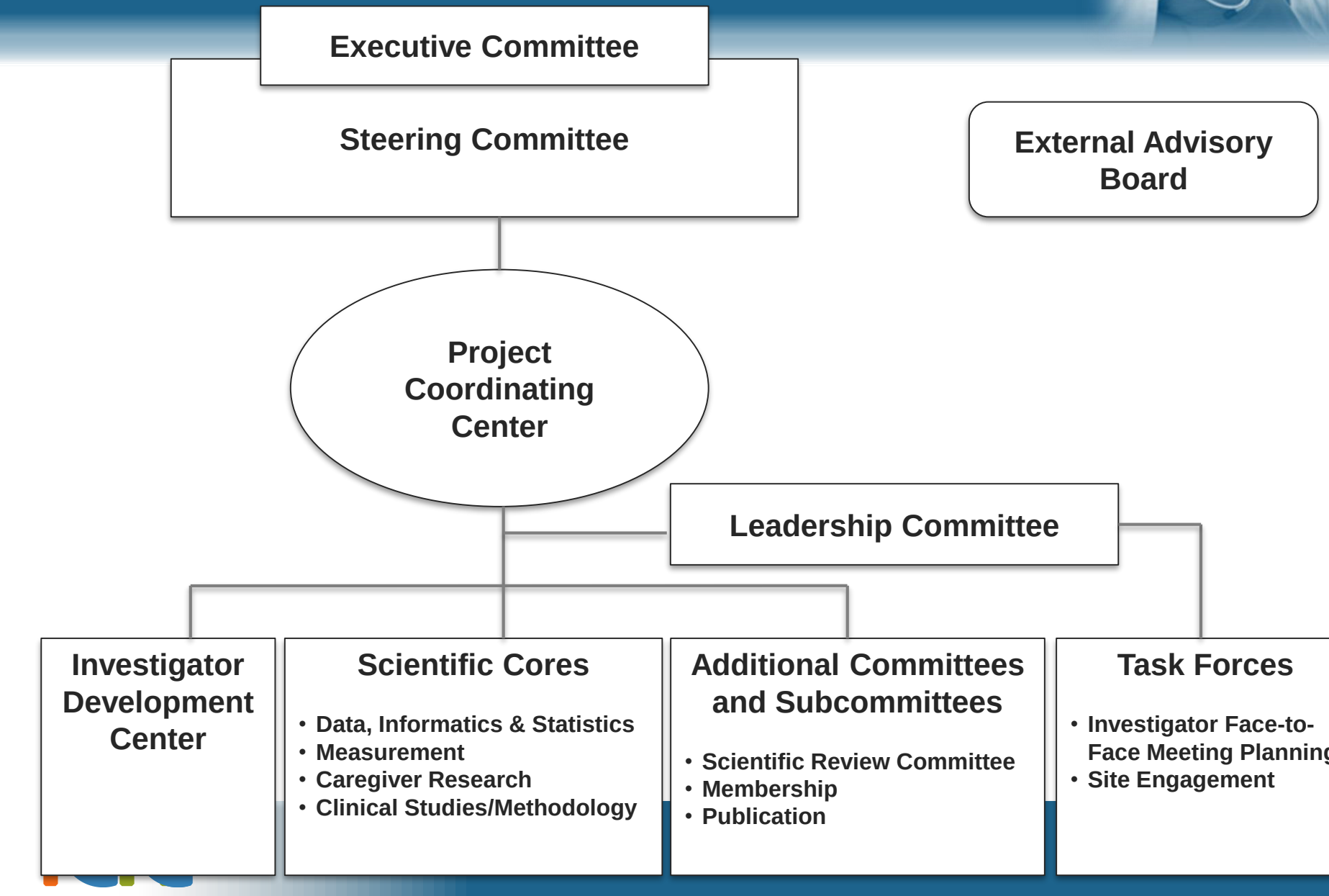
Excellent palliative care relies on best evidence and a scientific underpinning. The PCRC exists to lead, catalyze, and empower a community of investigators who are developing an evidence base to ensure high quality care and optimal well-being for persons with serious illness and their caregivers.

PCRC Mission *(revised Aug 2017)*

The mission of the PCRC is to support the conduct of high quality, effective palliative care clinical research by:

- Supporting investigators at all levels of experience in the conduct of clinical studies;
- Conducting nationally representative, multi-institutional studies that include diverse populations;
- Leveraging Standardized Data Elements and a de-identified palliative care study data repository that amplifies the impact of any single study;
- Providing methodological resources, participant access/recruitment, and the expertise of PCRC investigators from multiple disciplines.

PCRC Leadership and Organizational Structure



PCRC Executive Committee

Jean Kutner

(*University of Colorado*)

PCRC Group Co-Chair, Contact Principal Investigator, Project Coordinating Center Lead

Christine Ritchie

(*Massachusetts General Hospital*)

PCRC Group Co-Chair, Investigator Development Center Lead

Kathryn Pollak

(*Duke University*)

PCRC Group Co-Chair, Clinical Studies and Methodology Core Lead

PCRC Leadership – Cores and Committees

Data Informatics & Statistics Core

Katie Colborn
Director
Univ of Colorado

Salimah Meghani
Co Dir / Qualitative Lead
Univ of Pennsylvania

Caregiver Research Core

Betty Ferrell
Director
City of Hope

Nick Dionne-Odom
Consultant
UAB

Director, Site Engagement

Stacy Fischer
Univ of Colorado

Measurement Core

Antonia Bennett
Director
UNC

Laura Hanson
Co-Director
UNC

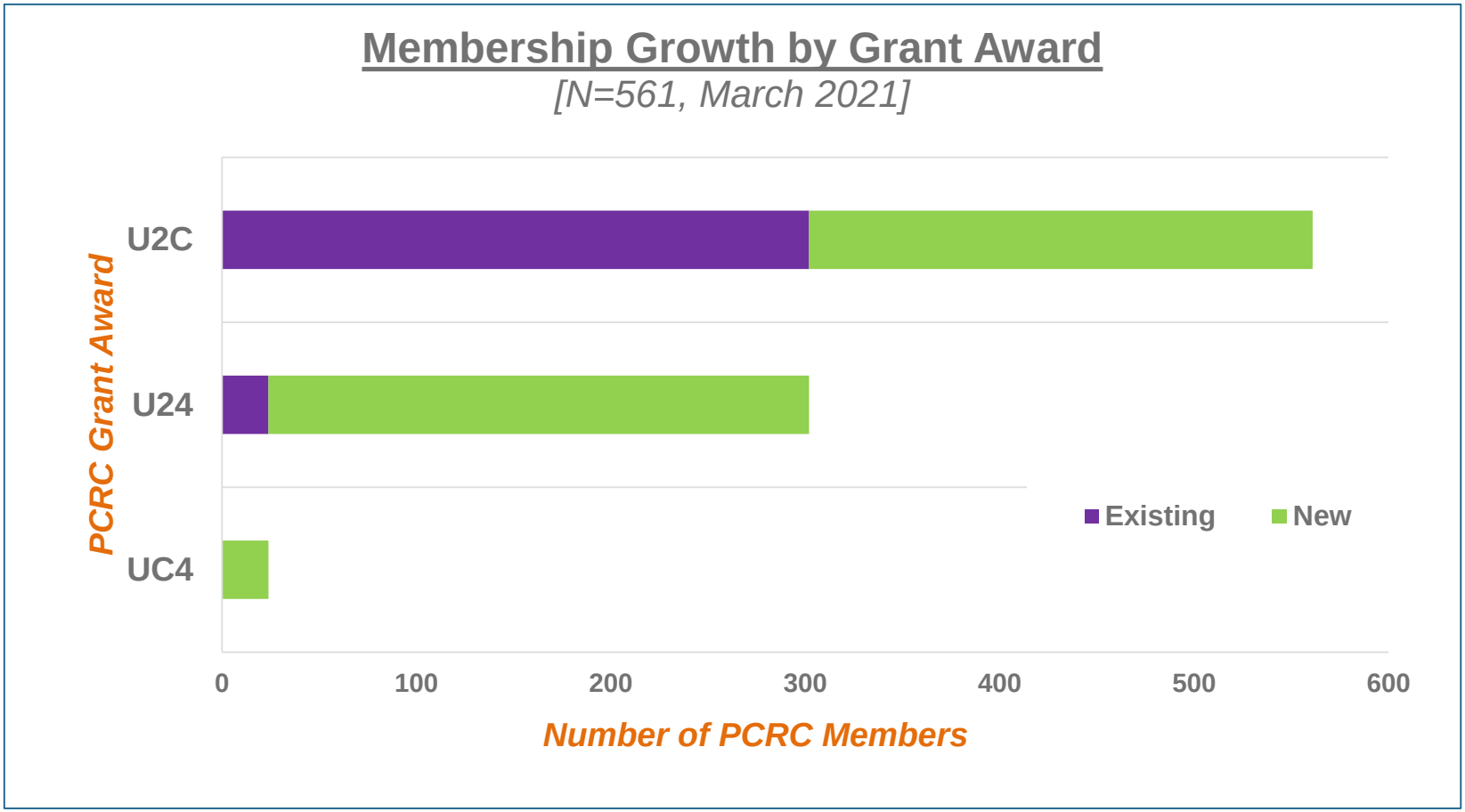
Clinical Studies / Methodology Core

Tammy Somers
Co-Director
Duke

Director, Pilot Program

Laura Porter
Director,
Pilot Program

PCRC Membership Metrics

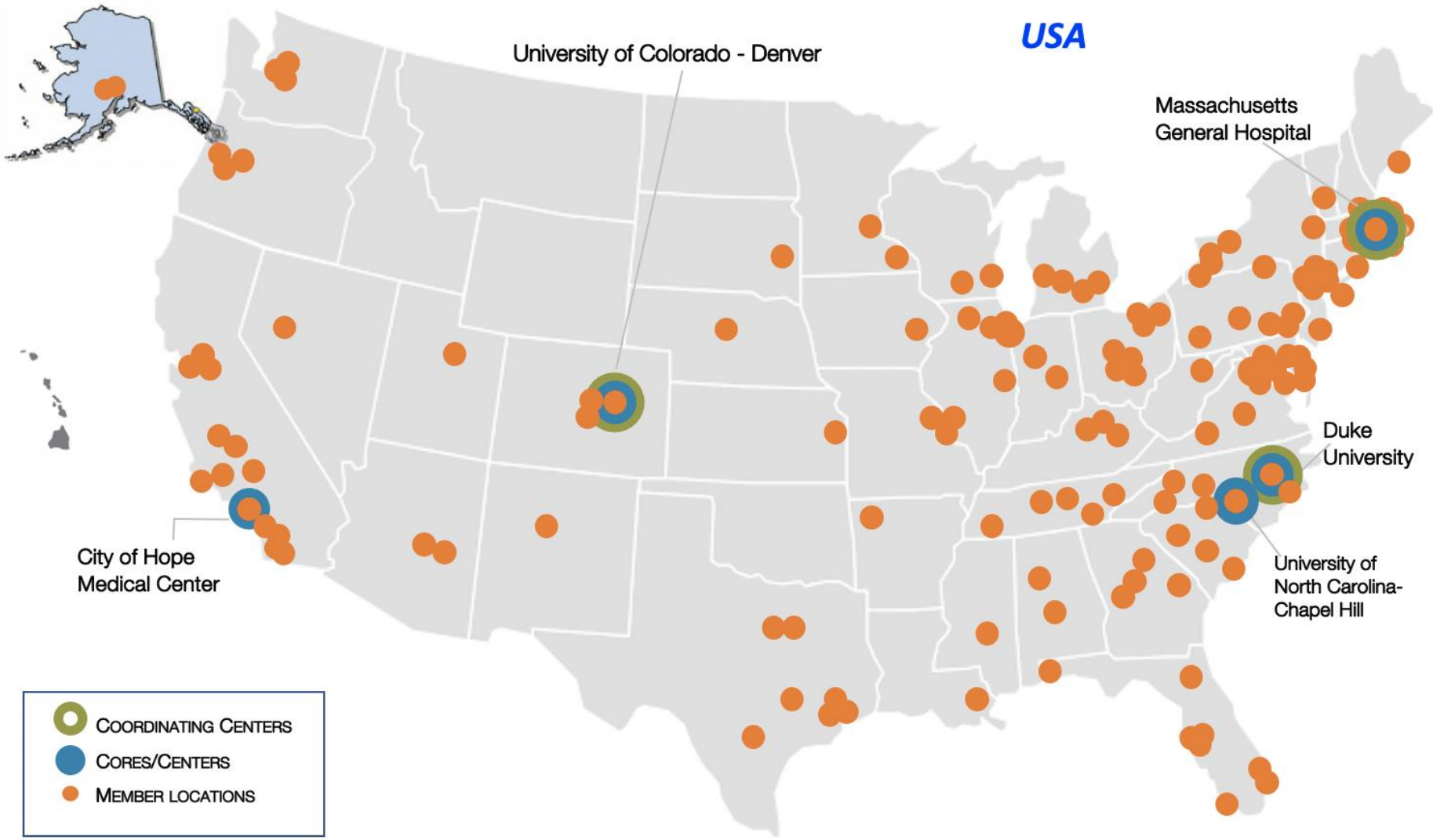


As of Mar 2021

http://palliativecareresearch.org/members/interested-in-pcrc-membership/summary-of-pcrc-members/

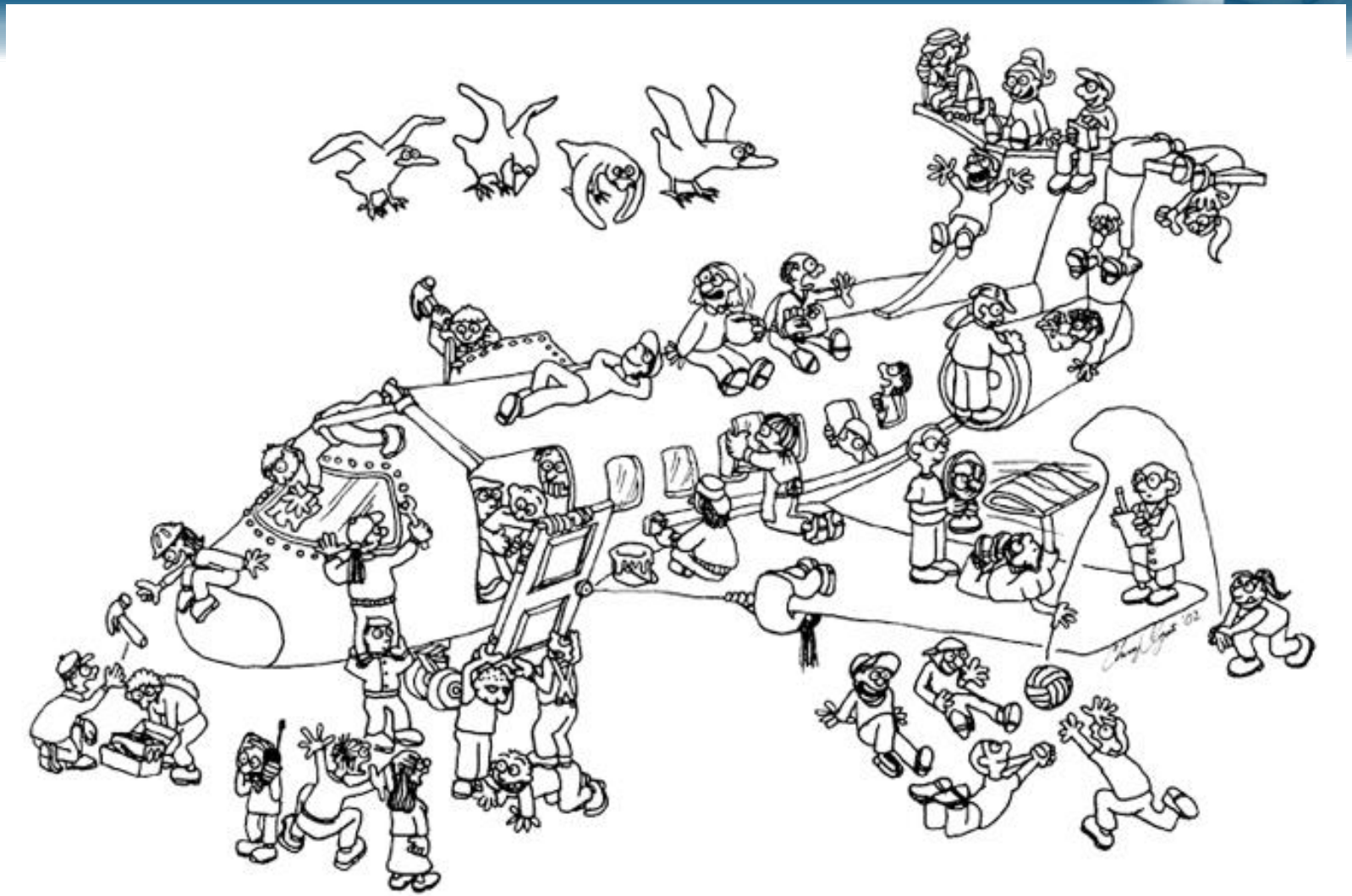
Member Locations [n=193]

As of Mar 2021



Total # countries = 11

Statin discontinuation trial – brief overview

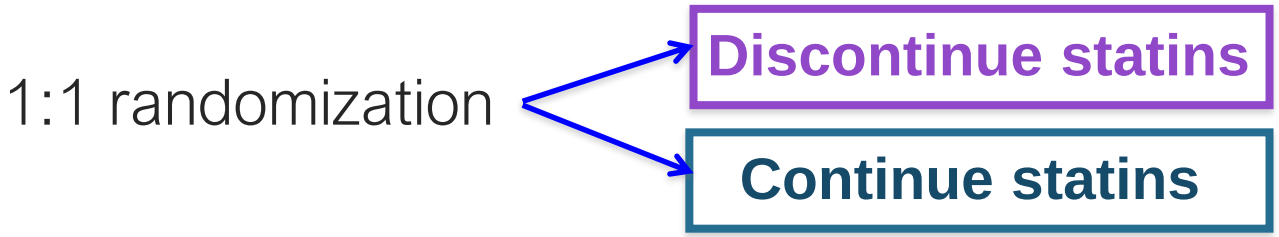


Research Question

Is it safe to discontinue statins for patients with less than one year to live?

Design Overview

Multicenter, unblinded pragmatic trial



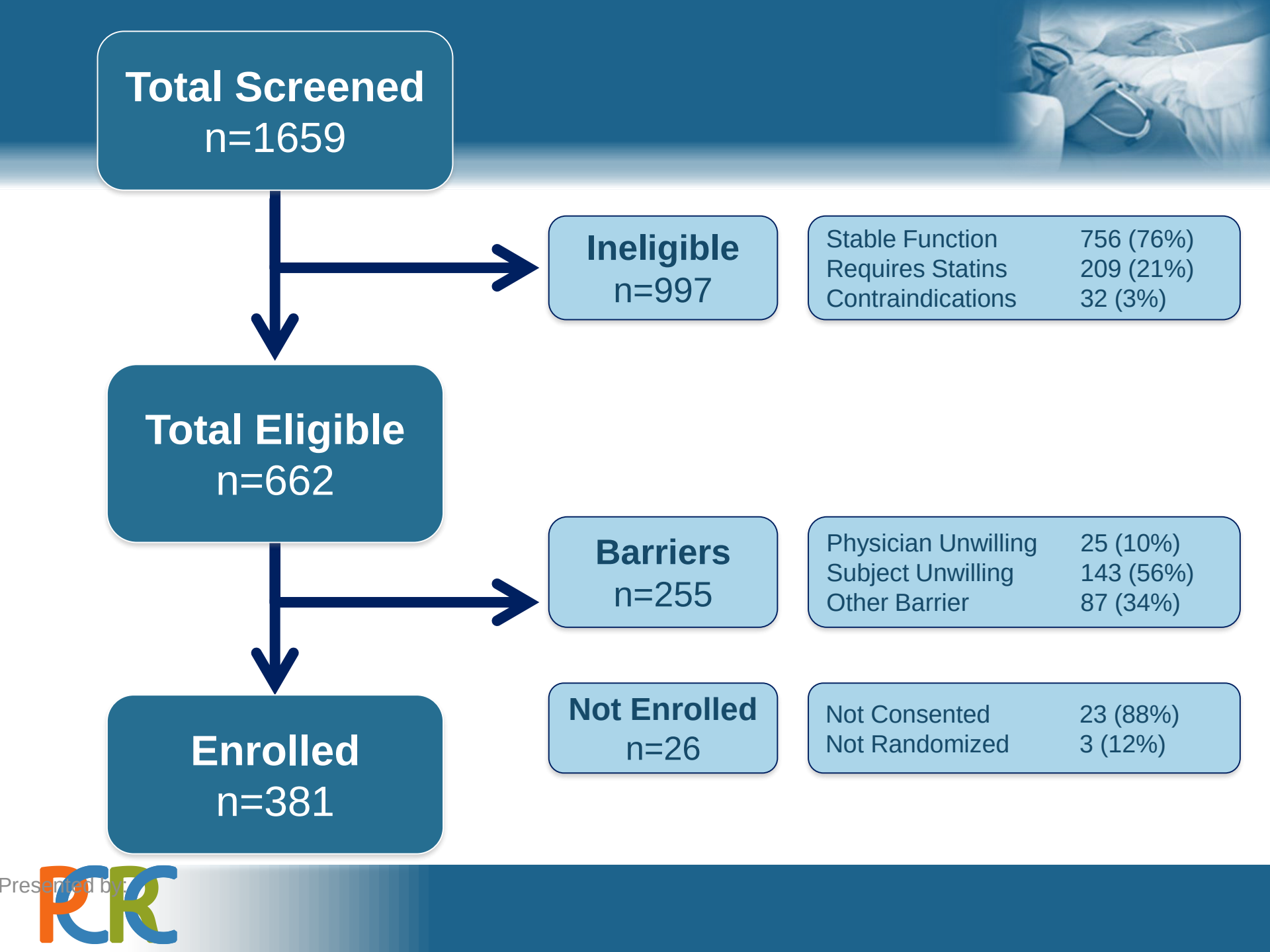
- **Outcomes** @ baseline & at least monthly, following patients for up to a year:
  - Survival
  - Cardiovascular events
  - Quality of life (QOL, McGill) and symptoms (ESAS+)
  - Number of medications other than statins being taken
  - Health resource utilization and cost

Inclusion Criteria

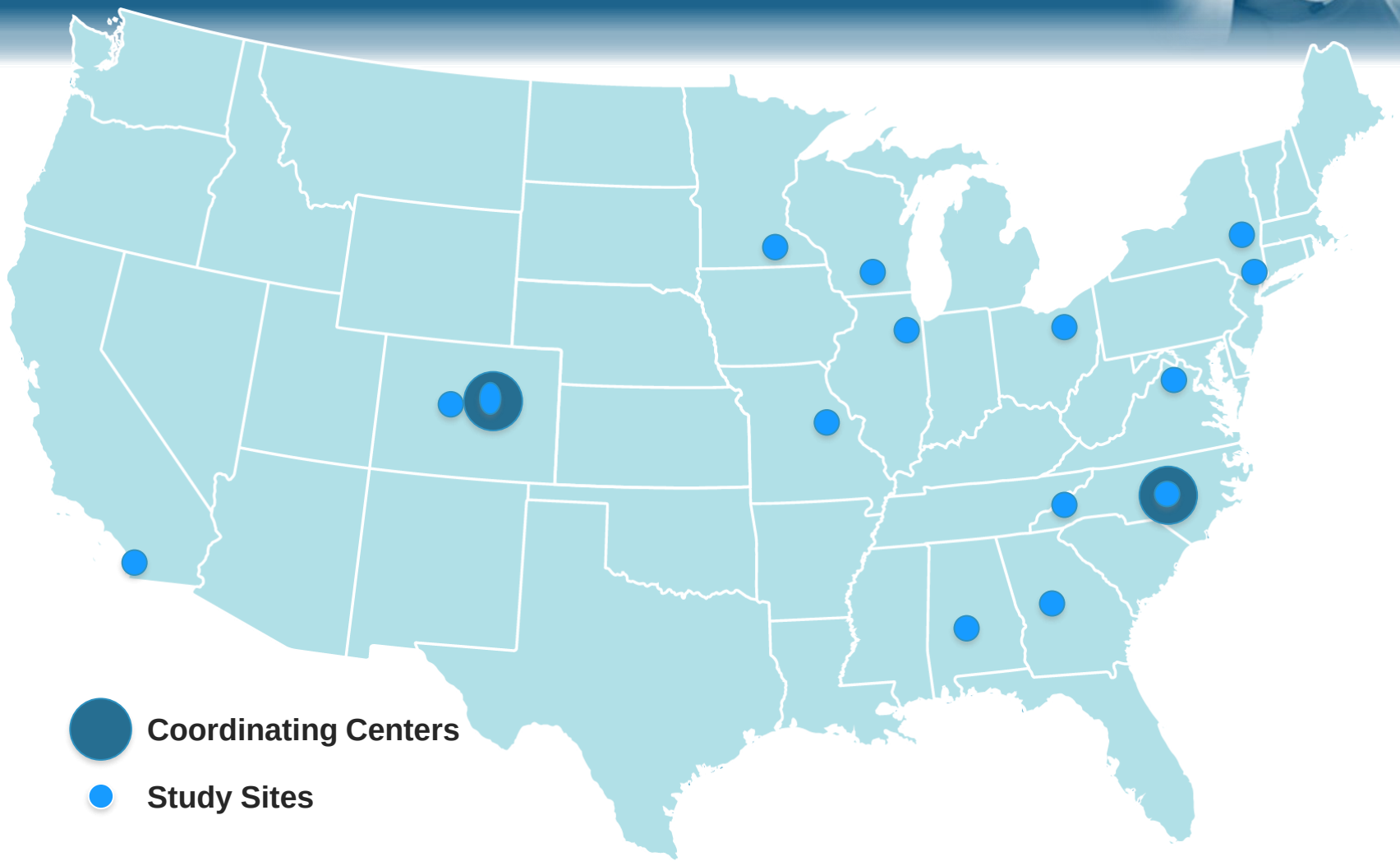
- English-speaking adults, > 3 months on a statin
- Advanced, life-limiting disease, defined as:
  - Treating MD 'would not be surprised if the patient died within a year"
  - Life expectancy of >1 month
  - Decline in AKPS to <80% in last 3 months
- Cognitively intact or legally-authorized proxy

Exclusion Criteria

- Known CV disease (or sufficient risk) requiring maintenance of statins
- Symptoms of myositis
- Liver function tests or CK > 2.5x upper limits of normal
- Other contraindications to continuing statins
- Patient/proxy unwilling/unable to provide consent
- Treating MD unwilling to allow enrollment


Total Screened
n=1659
Ineligible
n=997
Stable Function 756 (76%)
Requires Statins 209 (21%)
Contraindications 32 (3%)
Total Eligible
n=662
Barriers
n=255
Physician Unwilling 25 (10%)
Subject Unwilling 143 (56%)
Other Barrier 87 (34%)
Not Enrolled
n=26
Not Consented 23 (88%)
Not Randomized 3 (12%)
Enrolled
n=381

15 Participating PCRC Sites



***Diversity Includes SON, SPH, CCC, minority patient populations*

Analysis

- Descriptive summaries, intention-to-treat approach
- Safety analyses, non-inferiority hypothesis
- Time to event
- Patient-centered outcomes
  - AUC: baseline – 20 weeks
  - Mixed effects model w/ maximum-likelihood estimates for missing data
- 381 patients enrolled
  - 189 discontinued; 192 continued
- Median followup (Q1, Q3) = 18 weeks (5, 23)

Top Line Results

381 Patients

- 189 Discontinued statins
- 192 Continued statins

Age=74y; 45% female; 49% cancer; 69% >5y on statins

Rate of death within 60 days:

Discontinued statins	23.8%
Continued statins	20.3%

P=0.36

https://pubmed.ncbi.nlm.nih.gov/25798575/ (JAMA Int Med; 2015)

Lessons Learned: Study Start Up

- Rebudgeting
  - Initial proposed budget cut by 25%
- IRB
- Site and Site PI selection and training
- Outcome(s) and measure selection

Study Start Up: IRB

Special Series on Research Methodology

Ethical Conduct of Palliative Care Research: Enhancing Communication Between Investigators and Institutional Review Boards

Amy P. Abernethy, MD, PhD, Warren H. Capell, MD, Noreen M. Aziz, MD, PhD, MPH, Christine Ritchie, MD, MSPH, Maryjo Prince-Paul, PhD, APRN, ACHPN, FPCN, Rachael E. Bennett, MA, and Jean S. Kutner, MD, MSPH

Duke Clinical Research Institute (A.P.A.) and Duke Cancer Institute (A.P.A.), Duke University School of Medicine, Durham, North Carolina; University of Colorado School of Medicine (W.H.C., R.E.B., J.S.K.), Aurora, Colorado; Division of Extramural Activities (N.M.A.), National Institute of Nursing Research, National Institutes of Health, Bethesda, Maryland; University of California at San Francisco (C.R.), San Francisco, California; and Frances Payne Bolton School of Nursing (M.P.-P.), Case Western Reserve University, Cleveland, Ohio, USA

Abstract

Palliative care has faced moral and ethical challenges when conducting research involving human subjects. There are currently no resources to guide institutional review boards (IRBs) in applying standard ethical principles and terms—in a specific way—to palliative care research. Using as a case study a recently completed multisite palliative care clinical trial, this article provides guidance and recommendations for both IRBs and palliative care investigators to facilitate communication and attain the goal of conducting ethical palliative care research and protecting study participants while advancing the science. Beyond identifying current challenges faced by palliative care researchers and IRBs reviewing palliative care research, this article suggests steps that the palliative care research community can take to establish a scientifically sound, stable, productive, and well-functioning

https://pubmed.ncbi.nlm.nih.gov/24879998/

Study Start Up: Site and Site PI Selection

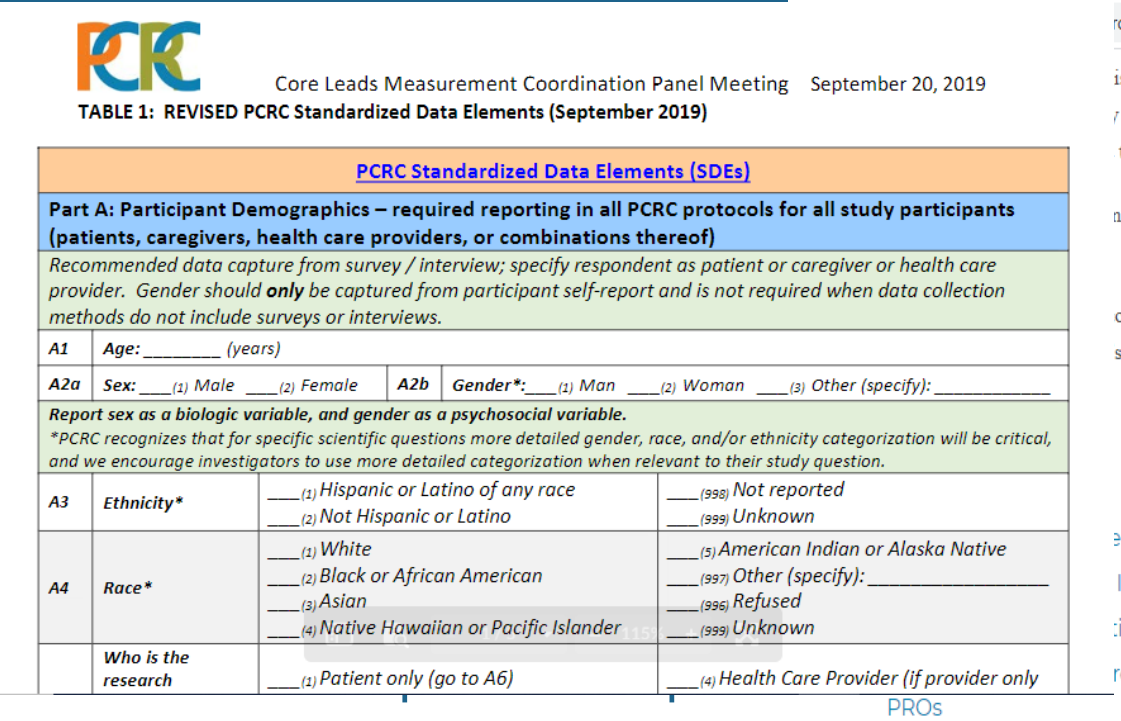
- **Site Characteristics**
  - What type of care settings will be used as recruitment sites at your study site?
  - Who are the gatekeepers and champions in each of these settings?
  - What systems are in place to identify potential study participants?
  - What are some known hurdles you will have to overcome to subject recruiting? E.g.:
    - Administrative hoops (e.g., IRB, other oversight committees, access to medical records, etc.).
    - Political issues – relationship building is key
    - Getting buy-in from people who are already too busy
    - Approaching potential study participants who are facing a life-limiting illness

- **Site PI Characteristics**
  - Is it the right site PI? Enthusiasm is not synonymous with effectiveness

- **Hire the right CRCs**
  - Recruiting is a specialized skill, especially in palliative care research

- **Train, re-train and re-train again**

Outcome: PCRC refined its Site PI and study site selection process, asking more in depth questions and seeking commitments (https://palliativecareresearch.org/index.php/research/investigator-support-information/collaborating-pcrc)



Core Leads Measurement Coordination Panel Meeting September 20, 2019

TABLE 1: REVISED PCRC Standardized Data Elements (September 2019)

PCRC Standardized Data Elements (SDEs)			
Part A: Participant Demographics – required reporting in all PCRC protocols for all study participants (patients, caregivers, health care providers, or combinations thereof)			
*Recommended data capture from survey / interview; specify respondent as patient or caregiver or health care provider. Gender should **only** be captured from participant self-report and is not required when data collection methods do not include surveys or interviews.*			
A1	**Age:** _____ *(years)*		
A2a	**Sex:** ___(1) Male ___(2) Female	**A2b**	**Gender*:** ___(1) Man ___(2) Woman ___(3) Other (specify): _____
Report sex as a biologic variable, and gender as a psychosocial variable. **PCRC recognizes that for specific scientific questions more detailed gender, race, and/or ethnicity categorization will be critical, and we encourage investigators to use more detailed categorization when relevant to their study question.*			
A3	**Ethnicity***	___(1) Hispanic or Latino of any race ___(2) Not Hispanic or Latino	___(998) Not reported ___(999) Unknown
A4	**Race***	___(1) White ___(2) Black or African American ___(3) Asian ___(4) Native Hawaiian or Pacific Islander	___(5) American Indian or Alaska Native ___(997) Other (specify): _____ ___(996) Refused ___(999) Unknown
	Who is the research	___(1) Patient only (go to A6)	___(4) Health Care Provider (if provider only

rch.org/corescenters/measurement-core

istics of survey data collection, including the mode and method of data capture (self or
paper, tablet, or web; in clinic or at home), the frequency of assessments and reminders,
training of site staff and survey respondents.

n portions of protocol text, consent forms, and IRB applications regarding survey data

orrect scoring algorithm for survey instruments and provide this to the Data & Statistics Core
s statistician.

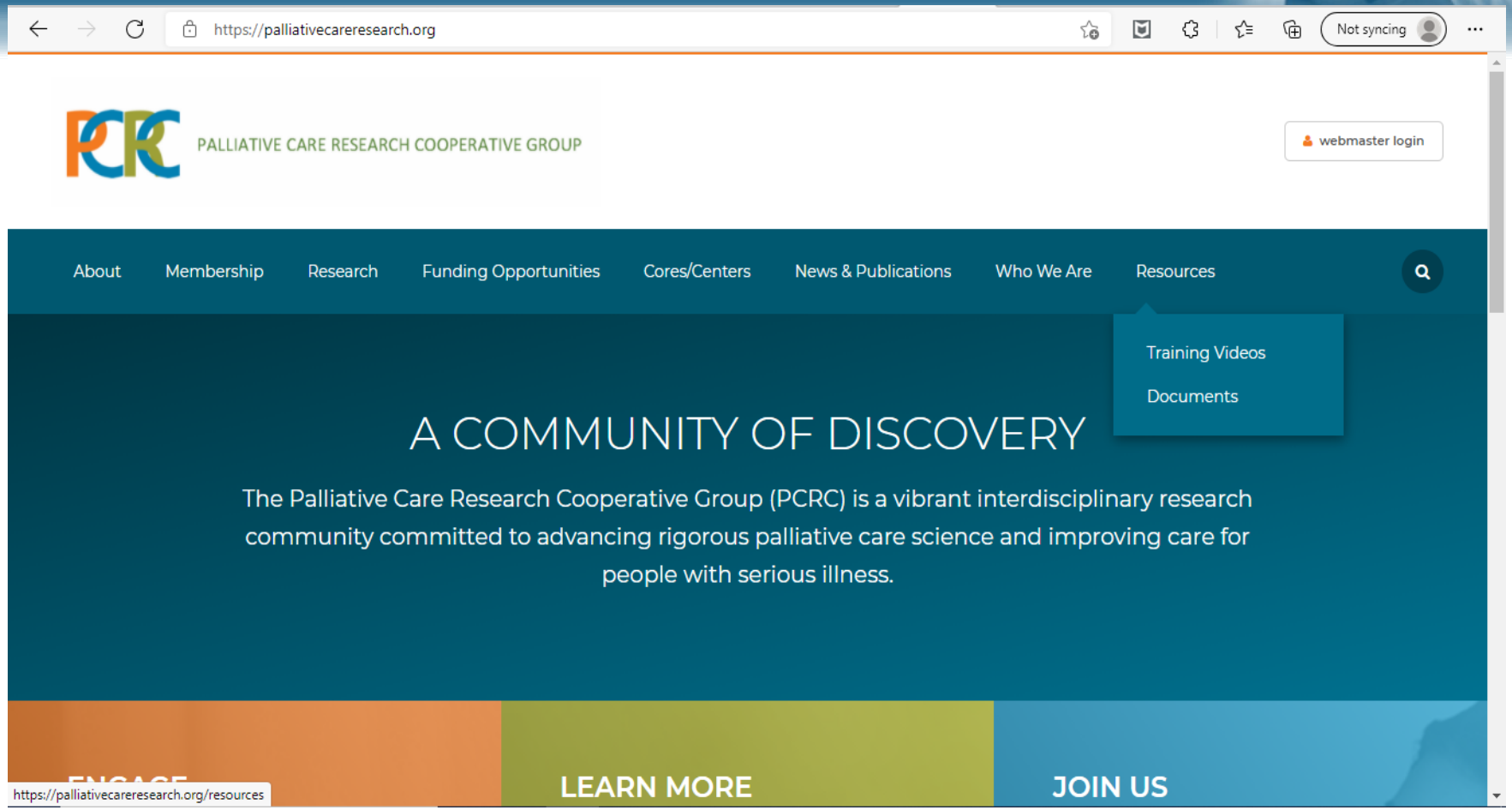
ement Tool Library
Instruments Relevant to Palliative Care
ient Reported Outcomes (PROs) in your research studies
resources when designing studies and conducting research that includes
PROs

- PCRC Resources (now) available:
  - https://palliativecareresearch.org/corescenters/measurement-core
  - https://palliativecareresearch.org/index.php/corescenters/data-informatics-statistics-core-disc/pcrc-standardized-data-elements

Lessons Learned: Study Conduct

- Recruitment
- Site performance:
  - Site payment
  - When to add new sites and when to retire existing sites
- DSMB: Primary study endpoint change
- Adverse event definition and adjudication
  - Definitions and rules changed after study start up

Recruitment



Recruitment

https://palliativecareresearch.org/resources/training-videos

Not syncing

Training Videos

We have created some training videos that can be used to help you with several important discussions that occur when conducting PCRC studies.

We have created some training videos that can be used to help you with several important discussions that occur when conducting PCRC studies.

To view our video channel please visit https://vimeo.com/channels/pcrcgroup.

ANNOUNCEMENTS

- NINR Director's Lecture: 9/14/21 10-11 am ET
- JAMA Special Communication
- HARVARD MEDICAL SCHOOL WORKSHOP ON RESEARCH METHODS IN SUPPORTIVE ONCOLOGY
- Clin-STAR funding opportunity notice
- NIH COVID-19 RADx-UP Opportunities

TWEETS FROM @PCRCGROUP

Tweets by @PCRCGroup

Recruitment

https://palliativecareresearch.org/resources/documents

Not syncing

To download a copy of the needed document, please click on the link. Please note: you do not need an account nor do you need to log in to download these documents.

Grant Preparation Phase:

- PCRC Grant Resource for Protection of Human Subjects
- PCRC Resources - Scientific Environment
- PCRC Protocol Guidelines
- Grant-related information for contracting
- PCRC Data Sharing Plan

Study Conduct:

- PCRC Recruitment Innovation Initiative- Participant and Provider Recruitment Measures
- PCRC Recruitment Innovation Initiative- Financial Consideration
- Clinical Research Coordinator (CRC) Handbook
- Authorship Protocol v2.0
- Conflict of Interest Information

Social Determinants of Health (SDoH)-related materials

ANNOUNCEMENTS

NINR Director's Lecture: 9/14/21 10-11 am ET

JAMA Special Communication

HARVARD MEDICAL SCHOOL WORKSHOP ON RESEARCH METHODS IN SUPPORTIVE ONCOLOGY

Clin-STAR funding opportunity notice

NIH COVID-19 RADx-UP Opportunities

TWEETS FROM @PCRCGROUP

Tweets by @PCRCGroup

PCRC Group
@PCRCGroup
Mi-Kyung Song is presenting the next NINR Director's Lecture on September 14, 2021 from 10:00 am - 11:00 am. Click here for more information: ninr.nih.gov/newsandinforma...

Aug 10, 2021

Appendices

Original Article

Strategies to Support Recruitment of Patients With Life-Limiting Illness for Research: The Palliative Care Research Cooperative Group

Laura C. Hanson, MD, MPH, Janet Bull, MD, Kathryn Wessell, BA, Lisa Massie, BA, Rachael E. Bennett, MA, Jean S. Kutner, MD, MSPH, Noreen M. Aziz, MD, PhD, MPH, and Amy Abernethy, MD

Division of Geriatric Medicine and Palliative Care Program (L.C.H.) and Cecil B. Sheps Center for Health Services Research (L.C.H., K.W.), University of North Carolina, Chapel Hill, North Carolina; Four Seasons Hospice and Palliative Care (J.B., L.M.), Flat Rock, North Carolina; Division of General Internal Medicine (R.E.B., J.S.K.), Department of Medicine, University of Colorado School of Medicine, Denver, Colorado; National Institute of Nursing Research (N.M.A.), National Institutes of Health, Bethesda, Maryland; and Division of Oncology (A.A.), Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA

Abstract

Context. The Palliative Care Research Cooperative Group (PCRC) is the first clinical trials cooperative for palliative care in the U.S.

Objectives. To describe barriers and strategies for recruitment during the inaugural PCRC clinical trial.

Methods. The parent study was a multisite randomized controlled trial enrolling adults with life expectancy anticipated to be one to six months, randomized to discontinue statins (intervention) vs. to continue on statins (control). To study recruitment best practices, we conducted semistructured interviews with 18 site principal investigators (PIs) and clinical research

https://pubmed.ncbi.nlm.nih.gov/24863152/

Site Performance

Table 1 - Study Enrollment

Table 1.1 - Timeline of Planned Enrollment

Site	Site Start Date	IRB Approved N	Target N	Target Months for Enroll	Target Enroll Rate	Actual N	Actual Months Enroll	Actual Enroll Rate	Future N Still Needed	Future Months for Enroll	Future Enroll Rate
01 - [redacted]	2011-06-03	132	120	18.0	6.7	50	13.0	3.8	70	5.0	13.9
02 - [redacted]	2011-06-22	120	120	17.4	6.9	30	12.4	2.4	90	5.0	17.9
03 - [redacted]	2011-08-23	100	80	15.4	5.2	16	10.3	1.5	64	5.0	12.7
04 - [redacted]	2011-10-07	120	120	13.9	8.6	23	8.9	2.6	97	5.0	19.3
05 - [redacted]	2011-08-31	110	120	15.1	7.9	11	10.1	1.1	109	5.0	21.7
06 - [redacted]	2011-11-17	120	110	12.6	8.8	1	7.5	0.1	109	5.0	21.7
07 - [redacted]	2011-11-18	120	120	12.5	9.6	5	7.5	0.7	115	5.0	22.9
08 - [redacted]	2011-12-20	80	80	11.5	7.0	4	6.4	0.6	76	5.0	15.1
09 - [redacted]	2011-12-09	110	100	11.8	8.5	2	6.8	0.3	98	5.0	19.5
10 - [redacted]	2012-04-12	144	120	7.7	15.5	1	2.7	0.4	119	5.0	23.7
11 - [redacted]	2011-09-14	140	110	14.7	7.5	1	9.6	0.1	109	5.0	21.7
Total	2011-09-03	1,296	1,200	15.0	79.9	144	10.0	14.4	1056	5.0	210.1

The study start date is 2011-06-03 (date first site received IRB approval).
The date enrollment is planned to end is 2012-12-03 (18 months after the study start date).

Site Performance

Table 1.1 - Timeline of Planned Enrollment

Site	Target N	Target Months for Enroll	Target Enroll Rate	Actual N	Actual Enroll Rate	Rate Last 3 Months
01 -	109	22.9	4.8	109	4.8	7.3
02 -	45	22.3	2.0	47	2.1	1.7
03 -	42	20.2	2.1	43	2.1	3.7
04 -	37	18.8	2.0	46	2.4	4.0
05 -	46	20.0	2.3	51	2.5	5.7
06 -	4	17.4	0.2	4	0.2	0.3
07 -	9	17.4	0.5	14	0.8	1.3
08 -	16	16.3	1.0	9	0.6	0.0
09 -	14	16.7	0.8	18	1.1	0.7
10 -	1	12.6	0.1	1	0.1	0.0
11 -	1	19.5	0.1	1	0.1	0.0
12 -	11	8.3	1.3	5	0.6	0.7
13 -	11	6.5	1.7	16	2.5	2.7
14 -	6	6.5	0.9	9	1.4	0.7
15 -	8	3.7	2.2	2	0.5	0.7
Total	360	19.9	18.1	375	18.8	29.3

The study start date is 2011-06-03 (date first site received IRB approval).
The date enrollment is planned to end is 2013-04-30.

DSMB: Primary Study Endpoint Change

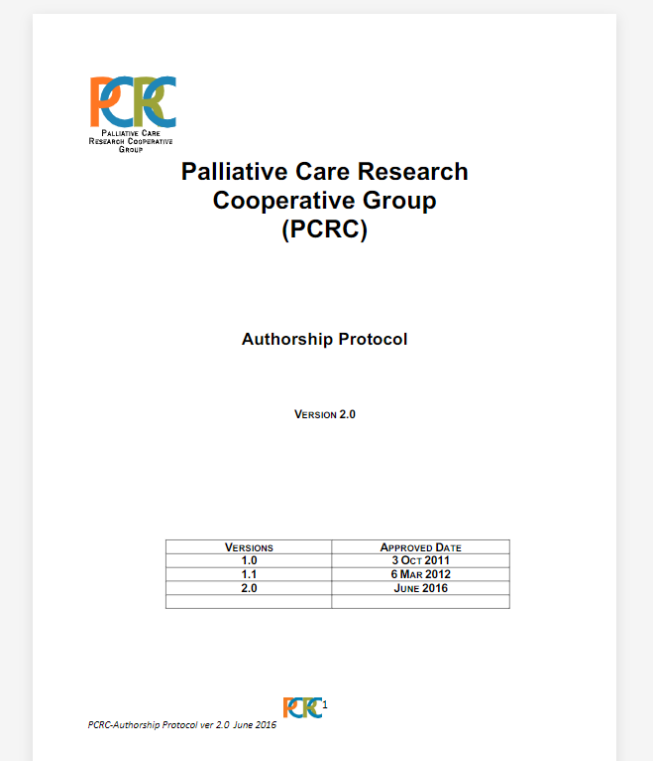
- Original Endpoint: Median Survival
  - Original estimated median survival = 3 months; Sample size =1200
  - Interim analysis median survival = 9 months; Revised sample size estimate >30,000
- Discussions begun with DSMB ~15 months post study start
- Months 15 – 17: scenario development; ongoing discussion
- Month 17: DSMB approved revised primary endpoint:
  - Death within 60 days of enrollment; Sample size = 360
  - Communicated to NINR; NINR approval obtained

Adverse Event Reporting

- Differentiate AEs from predefined study outcomes:
  - Hospital admissions
  - Emergency department visits
  - New CV events
  - Invasive procedures for cardiac events
  - Venous thromboembolism
  - Pneumonia
- Create event adjudication committee to evaluate for relatedness to trial intervention
- Consider what data will be available in study population
- Keep tabs on changing environment – FDA AE reporting categories changed ~ 3 months after initiated study enrollment

Lessons Learned: Publications

- Publications guidelines / standard operating procedures



Palliative Care Research Cooperative Group

Palliative Care Research Cooperative Group (PCRC)

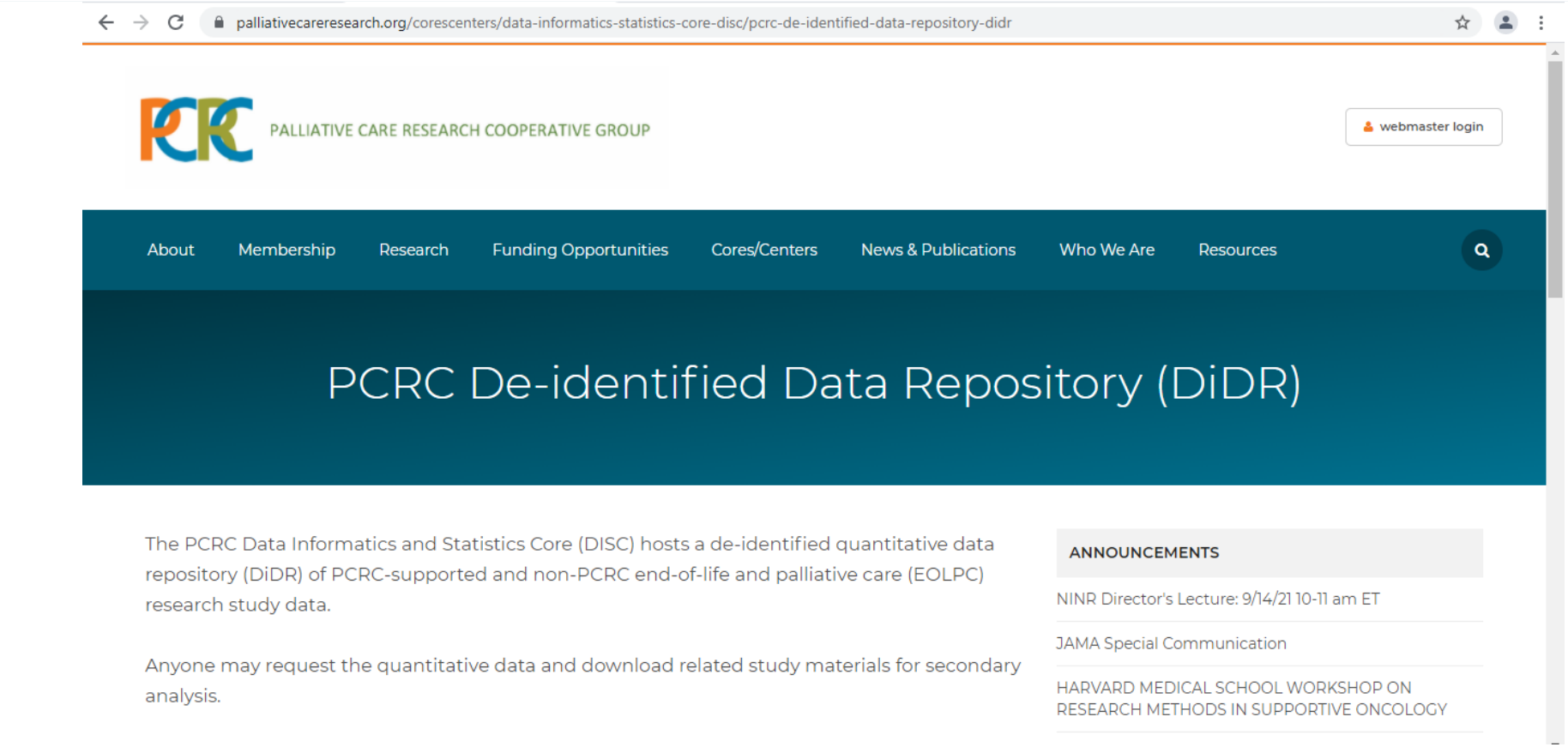
Authorship Protocol

VERSION 2.0

VERSIONS	APPROVED DATE
1.0	3 OCT 2011
1.1	6 MAR 2012
2.0	JUNE 2016

- Multi-author paper editing/revision approach
- Mapping out publications, authors and accountability

Lessons Learned: De-identified data repository and secondary data analysis



JAMA Network

JAMA Internal Medicine

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Comment & Response

January 2019

Coding Error Resulting in Change in Secondary Outcome Scores in Trial of Safety and Benefit of Discontinuing Statin Therapy Among Terminally Ill Patients

Jean S. Kutner, MD, MSPH[1]; Amy P. Abernethy, MD, PhD[2]

» Author Affiliations

JAMA Intern Med. 2019;179(1):126. doi:10.1001/jamainternmed.2018.7162

https://pubmed.ncbi.nlm.nih.gov/30508023/

Summary

- Start up
  - Rebudgeting
  - IRB
  - Site and Site PI recruitment and training
  - Outcome(s) and measure selection
- Conduct
  - Recruitment
  - Site performance
  - DSMB role/ Primary study endpoint change
  - Adverse event definition and adjudication
- Publications – primary and secondary
- De-identified data repository and secondary data analysis

Lessons learned from conduct of the statin deprescribing trial have shaped formation of the PCRC and its resources.

PCRC contacts

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