RESEARCH PROJECT COOPERATIVE AGREEMENT **Federal Award Date:** 08/10/2015

Department of Health and Human Services
National Institutes of Health
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Grant Number: 1U01HL125388-01A1
FAIN: U01HL125388

Principal Investigator(s):
DAVID A ASCH, MD

Project Title: ICOMPARE-CCC

Ms. Elizabeth Peloso
AssocVicePres/AssocViceProvost for Research
University of Pennsylvania
Franklin Building
Suite P-221
Philadelphia, PA 191046205

Award e-mailed to: rs-award@lists.upenn.edu

Period Of Performance:
Budget Period: 08/12/2015 – 06/30/2016
Project Period: 08/12/2015 – 06/30/2019

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $1,518,991 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF PENNSYLVANIA in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number U01HL125388. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Beckie Chamberlin
Grants Management Officer
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Additional information follows

SECTION I – AWARD DATA – 1U01HL125388-01A1

Award Calculation (U.S. Dollars)

Salaries and Wages	$409,615
Fringe Benefits	$124,151
Supplies	$43,915
Travel Costs	$24,500
Other Costs	$92,067
Consortium/Contractual Cost	$363,194
Federal Direct Costs	$1,057,442
Federal F&A Costs	$461,549
Approved Budget	$1,518,991
Total Amount of Federal Funds Obligated (Federal Share)	$1,518,991
TOTAL FEDERAL AWARD AMOUNT	$1,518,991
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$1,518,991

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$1,518,991	$1,518,991
2	$1,564,276	$1,564,276
3	$1,293,630	$1,293,630
4	$1,276,257	$1,276,257

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Cardiovascular Diseases Research
CFDA Number:	93.837
EIN:	1231352685A1
Document Number:	UHL125388A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2015

IC	CAN	2015	2016	2017	2018
HL	8475150	$1,518,991	$1,564,276	$1,293,630	$1,276,257

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: SLSM N / **OC**: 414L / **Released**: CHAMBERLIB 08/05/2015
Award Processed: 06/15/2015 11:31:44 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1U01HL125388-01A1

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1U01HL125388-01A1

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

PI: **ASCH, DAVID A**	Title: ICOMPARE-CCC	
Received: 11/04/2014	FOA: PAR13-128	Council: 05/2015
Competition ID: FORMS-C	FOA Title: INVESTIGATOR INITIATED MULTI-SITE CLINICAL TRIALS (COLLABORATIVE R01)	
1 **U01 HL125388-01A1**	Dual:	Accession Number: 3758320
IPF: 6463801	Organization: UNIVERSITY OF PENNSYLVANIA	
Former Number: 1R01HL125388-01A1	Department: 4239 - DM-General Internal Med	
IRG/SRG: CLTR (MA)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 987,820 Year 2: 1,016,437 Year 3: 840,374 Year 4: 826,842	Animals: N Humans: Y Clinical Trial: Y Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N

Senior/Key Personnel:	*Organization:*	*Role Category:*
DAVID ASCH	The Trustees of the University of Pennsylvania	PD/PI
MATHIAS BASNER	The Trustees of the University of Pennsylvania	Co-Investigator
LISA BELLINI	The Trustees of the University of Pennsylvania	Co-Investigator
David Bates	BRIGHAM & WOMENS HOSPITAL	Other (Specify)-Subaward PI
DAVID DINGES	The Trustees of the University of Pennsylvania	Co-Investigator
Sanjay Desai	JOHNS HOPKINS UNIVERSITY	Other (Specify)-Subaward PI
Joel Katz	BRIGHAM & WOMENS HOSPITAL	Other (Specify)-Co-investigator
Daniel Mollicone	PULSAR INFORMATICS	Other (Specify)-Subaward PI
JUDY SHEA	The Trustees of the University of Pennsylvania	Co-Investigator
KEVIN VOLPP	The Trustees of the University of Pennsylvania	Co-Investigator

Appendices

icompareappendi

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

○ Pre-application ● Application ○ Changed/Corrected Application

4.a. Federal Identifier
HL125388

b. Agency Routing Number

2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number
1900-01-01	10049495	GRANT11775744

5. APPLICANT INFORMATION **Organizational DUNS*:** 0422507120000

Legal Name*: The Trustees of the University of Pennsylvania
Department: 4239 - DM-General Internal Med
Division:
Street1*: Office of Research Services
Street2: 3451 Walnut Street, Suite P-221
City*: Philadelphia
County: Philadelphia
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 19104-6205

Person to be contacted on matters involving this application
Prefix: First Name*: ELIZABETH Middle Name: D Last Name*: PELOSO Suffix:
Position/Title: AssocVicePres/AssocViceProvost for Research
Street1*: Franklin Building
Street2: Suite P-221
City*: Philadelphia
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 191046205
Phone Number*: 2157460234 Fax Number: 2158989708 Email: PennAORS@lists.upenn.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1231352685A1

7. TYPE OF APPLICANT* O: Private Institution of Higher Education

Other (Specify):
Small Business Organization Type ○ Women Owned ○ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

○ New ● Resubmission
○ Renewal ○ Continuation ○ Revision

If Revision, mark appropriate box(es).
○ A. Increase Award ○ B. Decrease Award ○ C. Increase Duration
○ D. Decrease Duration ○ E. Other *(specify)* :

Is this application being submitted to other agencies?* ○Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
ICOMPARE-CCC

12. PROPOSED PROJECT
Start Date* 07/01/2015
Ending Date* 06/30/2019

13. CONGRESSIONAL DISTRICTS OF APPLICANT
PA-002

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: DR. First Name*: DAVID Middle Name: A Last Name*: ASCH Suffix:

Position/Title: PROFESSOR A
Organization Name*: The Trustees of the University of Pennsylvania
Department: 4239 - DM-General Internal Med
Division: 4000 - SM-MG-School of Medicin
Street1*: BLOCKLEY HALL
Street2: Room 1223
City*: PHILADELPHIA
County: PHILADELPHIA
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 191046021
Phone Number*: 2158980102 Fax Number: Email*: ASCH@WHARTON.UPENN.EDU

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$6,016,067.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$6,016,067.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: SHEILA Middle Name: Last Name*: ATKINS Suffix:

Position/Title*: Associate Director
Organization Name*: The Trustees of the University of Pennsylvania
Department: 8760 - Research Services
Division:
Street1*: 3451 Walnut Street
Street2: P221 FRANKLIN BLDG
City*: PHILADELPHIA
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 191046205
Phone Number*: 2155736713 Fax Number: 215-573-8416 Email*: pennaors@lists.upenn.edu

Signature of Authorized Representative*
SHEILA ATKINS

Date Signed*
11/04/2014

20. PRE-APPLICATION File Name:Pre_Application.pdf

21. COVER LETTER ATTACHMENT File Name:Cover_Letter_Attachment.pdf

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 00004028

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	abstract.pdf
8. Project Narrative*	projplan.pdf
9. Bibliography & References Cited	ref.pdf
10.Facilities & Other Resources	Facilities_Upload.pdf
11.Equipment	
12. Other Attachments	StudyOrganizationAndAdmin.pdf
	ClusteredApplications.pdf

Funding Opportunity Number: PAR-13-128. Received Date: 2014-11-04T15:07:58.000-05:00

In the US and other countries, policy limiting duty hours in graduate medical education has undergone significant revision in the last decade and become a central point of debate. Evidence from human chronobiology and sleep argues for shorter shifts because fatigue leads to errors. However, evidence from operations research argues for more continuity because patient handoffs also lead to errors and may reduce the effectiveness of education necessary to produce independent clinicians. The evidence from both fields is compelling, resulting in uncertainty regarding how to best configure duty hour standards for fatigue management, high quality patient care, and trainee education. In 2011, the Accreditation Council for Graduate Medical Education (ACGME) imposed more restrictive duty hour standards for all trainees. The new duty hours added that post-graduate year 1 (PGY1) trainees (interns) work no more than 16h duty periods in a day. This change greatly increased the frequency of patient handoffs. As a result, alternative work schedules have been proposed that combine longer shifts to maintain continuity of patient care with efforts to manage fatigue.

We propose a cluster randomized trial of 58 Internal Medicine (IM) training programs to compare the current duty hour standards ("**Curr**" throughout this proposal) with a more flexible schedule ("**Flex**") that is grounded in contemporary understanding of sleep and patient safety and defined by three rules: [1] work no more than 80 hours per week; [2] call no more frequent than every 3rd night; [3] 1 day off in 7—all averaged over 4 weeks.

Our primary hypothesis addresses patient safety: *30-day patient mortality under* Flex *will not exceed (will not be inferior to) mortality under* Curr. Our secondary hypotheses address education and sleep and fatigue: (a) *Interns in* Flex *will spend greater time in direct patient care and education compared to interns in* Curr; (b) *Average daily sleep obtained by interns in* Flex *will not be less than (will not be inferior to) that of interns in* Curr.

iCOMPARE (Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education) will provide the rigorous comparative effectiveness data essential to setting duty hour policies that optimize quality of care and the competency of our future physicians. Moreover, the same two schedules, Curr vs. the novel Flex scheme, are being compared in the ongoing FIRST trial in residents in general surgery. **The combination of well-designed separate trials in both primarily procedural and non procedural fields will fill the unmet need for a high-quality, generalizable body of evidence to inform national duty hour policy.**

In US teaching hospitals, physicians in training care for patients under faculty supervision and are granted progressive autonomy and independence so that they may achieve independent practice upon completion of the program. While the US system of physician training is respected around the world, this multi-center national randomized controlled trial will determine how duty hours should be structured to optimize the quality of care in America's teaching hospitals as well as the competency of our future physicians.

Study Organization and Administration and Timeline

In accordance with NHLBI guidelines, the iCOMPARE study investigators are organized into two distinct but collaborating centers, the **Clinical Coordinating Center (CCC)**, at the University of Pennsylvania led by David Asch, and the **Data Coordinating Center (DCC)**, at the Johns Hopkins University led by James Tonascia. Each of these centers has separate areas of responsibility but will work together to achieve the aims of the project. The CCC will have primary responsibility to manage and implement the protocol; to recruit and manage the participating programs; to oversee the timely collection and quality control of relevant study data; to ensure compliance with IRB and other regulatory bodies; and to distribute supplies and funds as appropriate. The DCC will have primary responsibility to administer the randomization; receive and manage all study data; maintain a project website and facilitate project communications; prepare interim and final reports of the study's progress and results; and perform statistical analyses to support conclusions drawn from the study. The Centers will work together to establish and maintain quality assurance in the participating residency programs and to provide timely high-quality publications of the study's results. A figure below displays the organizational structure of the team conducting the trial.

A productive collaboration between the CCC and DCC toward a common mission has already developed. Many of the investigators have worked with each other in various organizational and investigational efforts, and the team has already shared successes in securing funding supporting a portion of the planned trial and waivers from the ACGME and in producing the letter of intent and two proposals to NIH. iCOMPARE also includes many other participants--program directors, trainees, and faculty. The study has launched a website (iCOMPAREstudy.com) already being used to build a community among these groups and to facilitate program recruitment. More than 50 programs have applied to be included in iCOMPARE and randomization will start in the Fall of 2014. Later, the website will host study news and a forum for participants to provide feedback on the process. We will use social media channels, including email, SMS, Twitter, and Facebook to push information individually or collectively about survey due dates, incentives, or other matters.

The primary leadership body for the trial will be a Steering Committee composed of key investigators from both the CCC and the DCC and a representative of the NHLBI; the ACGME does not plan to send a representative to the Steering Committee. The Steering Committee will appoint a smaller Executive Committee to facilitate decision making. A Data and Safety Monitoring Board, appointed by the NHLBI, will monitor the project, and an Advisory Board will be assembled to provide additional scientific input and guidance.

The **Steering Committee (SC)** is the principal decision-making body for iCOMPARE and will be chaired by David Asch, Principal Investigator of the CCC, with James Tonascia, PI of the DCC, serving as vice- chair. The remainder of the SC will be composed of core study team members from the CCC and the DCC and a representative of the NHLBI. The SC will have the responsibility to approve the project protocol and any subsequent amendments and to vote on other important decisions. A quorum of the SC will be seven members with decisions made by agreement of a majority of those participating. It is expected that the SC will appoint sub-committees, possibly to include non-members of the SC, to make recommendations in areas such as protocol implementation issues, publications, and ancillary studies. The SC will meet monthly by teleconference or in-person.

The **Executive Committee (EC)** will manage day-to-day issues in iCOMPARE and will be chaired by Sanjay Desai of the CCC, with Judy Shea of the CCC serving as vice-chair. It will make decisions between SC meetings, and will organize and prepare agendas for the SC meetings. The EC will be composed of a sub-group of the SC membership and will meet weekly by teleconference, although the frequency of meetings may vary depending on circumstance.

We anticipate the NHLBI will appoint a **Data and Safety Monitoring Board (DSMB)** which will be advisory to the NHLBI and will be charged with monitoring the project's performance as described in our monitoring plan. The DSMB will be expected to advise NHLBI periodically regarding the continuation of the study, including the possible recommendation of changes to the protocol. A draft **Data and Safety Monitoring Plan (DSMP)**, subject to review, modification, and approval by the DSMB, is included within the section on **Human Subjects**.

An **Advisory Board (AB)** will be appointed to make regular recommendations about the design and conduct of the project and will be chaired by Lisa Bellini of the CCC. The remaining AB members will not otherwise be part of the study team and will include the following leaders in graduate medical education, and policy: **Vineet**

Arora, MD, MA – Assistant Dean for Scholarship and Discovery at the University of Chicago and a national leader in medical education; **Ruth Benca, MD, PhD** – Professor of Psychiatry at the University of Wisconsin and past President of the Sleep Research Society and the Associated Professional Sleep Societies. **Karl Y Bilimoria, MD, MS** – a surgical oncologist at Northwestern who is leading an American Board of Surgery/American College of Surgeons-funded study on resident duty hours in surgical training; **Patrick Conway, MD** – Deputy Administrator of the Center for Medicare and Medicaid Services (CMS) and Director of the CMS Innovation Center in the US Department of Health and Human Services; **Michael ME Johns, MD** – Immediate past Chancellor of Emory University, Interim Executive Vice President for Health, University of Michigan, and Chair of the 2009 IOM Committee Report on Resident Duty Hours. The Advisory Board will make its reports directly to the Steering Committee. The AB is expected to meet semi-annually.

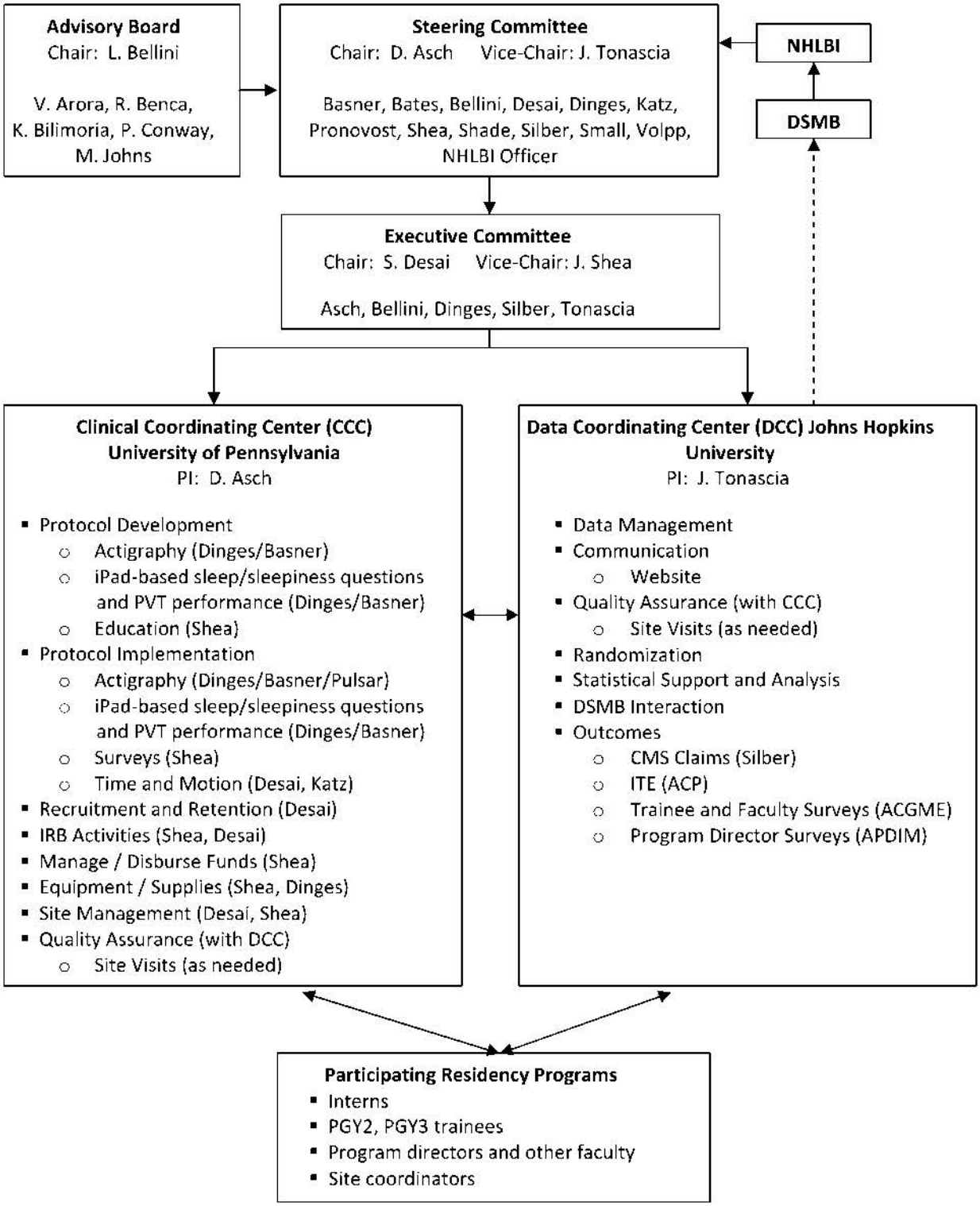
Program Directors from participating Internal Medicine residency programs represent site leaders for this multicenter trial. The CCC will host monthly conference calls for all participating program directors during the ramp up to the intervention start through the conclusion of the intervention period and ad hoc calls thereafter. Given the contributions required by participating program directors, efforts will be made to acknowledge them appropriately in publications as authors or other contributors as consistent with conventions and contributions.

The Program Directors at each of the eight sites involved in the Sleep and Alertness Substudy will identify a member of their staff to coordinate the distribution and rotation of the actiwatches, establish locations for and oversee the iPad PVT assessments, and serve as a liaison with the project managers based at the CCC. The program directors at each of the six sites involved in the Time and Motion Substudy will identify a member of their staff to coordinate the recruiting of observers and the identification of interns to be observed, in consultation and with the support of the project managers based at the CCC. The CCC will lead approximately weekly group calls among the coordinators at the sites participating in the Sleep and Alertness Substudy and approximately weekly group calls among the coordinators at the sites participating in the Time and Motion Substudy. The training of observers will be done by the CCC staff. The CCC project managers may visit these sites as needed to assist in these efforts. As noted in the budget, programs participating in these assessments will receive financial support to offset any costs of this participation.

The **Research Group** for iCOMPARE consists of investigators and staff from the CCC and the DCC, staff from the NHLBI, members of the Advisory Board and the DSMB, the Program Directors of the participating training programs, study coordinators based at the programs, and faculty and trainees participating in the project.

Oversight, responsibilities, data management and coordination of centers. The CCC and the DCC will share responsibility for oversight and management of the participating residency programs. The CCC will have the primary role coordinating protocol implementation at each program, and will review trainee duty schedules to ascertain compliance with the appropriate iCOMPARE intervention arm. The CCC will also coordinate implementation of the actigraphy and alertness iPad-based evaluations at the relevant sites, as well as the time and motion evaluations at the relevant sites, and will be responsible for training and data collection at those sites. The DCC will create and manage an internet-based data management system for the remote entry of survey, questionnaire, and other data to be collected from the sites, and for later merging those data with data from other sources (such as CMS claims data and ACGME education data). The DCC will also implement a data review system to perform quality assurance checks on data collected from the sites. As noted, the CCC will run monthly group calls with the program directors (and separate and weekly calls with site coordinators involved in the sleep and time motion evaluations). The CCC and DCC will together establish systems for monitoring protocol implementation and clinic performance, and for determining the composition and frequency of any "for cause" site visits.

iCOMPARE Organizational Structure



Project timeline. The project timeline is summarized in the following Gantt chart. Selected elements are annotated below.

	Pre Award	Funding Y1				Funding Y2				Funding Y3				Funding Y4				
		CY 2015				CY 2016				CY 2017				CY 2018				CY 2019
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
General Processes																			
Recruit programs																			
Hire new staff																			
Review of IRB approvals																			
Complete subcontracts																			
Support program rollout and function																			
Team mtgs																			
Advisory board mtgs																			
DSMB mtgs/conferences																			
Intervention period																			
Patient Safety and Costs Aims																			
Accumulate/process CMS data																			
Education Aims																			
Develop and pilot JIT instruments																			
Collect data JIT data																			
Develop and deploy end of year surveys																			
Obtain ACPTE data																			
Obtain ACGME data																			
Obtain APDIM data																			
Recruit 6 sites for Time Motion studies																			
Train and deploy Time Motion staff																			
Recruit interns and collect Time Motion data																			
Review and validate education data																			
Sleep Aims																			
Recruit 8 sites																			
Train staff at sites																			
Recruit interns and collect data																			
Review and validate sleep data																			
Analysis and Reporting																			
Prepare analytic files																			
Primary and secondary outcome analyses																			
Prepare manuscripts: methods/results																			
Prepare data sharing materials																			
Report to NIH																			

Notes to the timeline. If this application is successful, our start date for NIH funding will be July 1, 2015 and thus project years correspond to academic years. As noted, we have secured independent funding for the team to proceed prior to award and we will use that time to finish recruiting our sites and to begin hiring TBN staff. Our intervention period ends June, 2016, but our safety aims rely on Medicare data that become available approximately 9-10 months after the end of a calendar year. Complete study data are therefore available approximately October, 2017 (Y3Q2).

The timeline reflects elements like DSMB meetings that are based on our draft Data and Safety Monitoring Plan, but the DSMB may alter those draft plans.

We have paid particular attention to moving from research findings to dissemination as quickly and as effectively as possible. We will aim dissemination through traditional academic channels as well as new media. In particular, we will partner with the Leonard Davis Institute of Health Economics–an institute at the University of Pennsylvania that connects its School of Medicine (Perelman) to its business school (Wharton) and Schools of Nursing, Law, and Communication (Annenberg)—to extend the reach of our findings to members of Congress and leaders in health care who are unlikely to receive or read academic journals but who would value the results of this trial and are in positions to create change in other relevant areas. A recent analysis of 244 NHLBI-funded clinical trials revealed a median delay of 25 months between trial completion and publication of the main trial findings[1]. These results simultaneously reflect the realities of publication delay and also spur a call to action to overcome those delays in order to accelerate research impact. We aim to

produce results for portions of our study as early as Y3Q1, reflecting preliminary analyses of our sleep and activity work, and the time-motion studies of interns. But we expect to produce manuscripts describing research methods in advance of that. For other elements of the project we have allocated investigator time during the final months in order to concentrate efforts on analysis, dissemination, reach, and impact.

[1] Gordon D, Taddei-Petters W, Mascette A, Antman M, Kaufmann PG, Lauer MS. Publication of Trials Funded by the National Heart, Lung, and Blood Institute. N Engl J Med 2013; 369:1926-1934.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix: DR.
First Name*: DAVID
Middle Name: A
Last Name*: ASCH
Suffix:

2. Human Subjects

Clinical Trial? ○ No ● Yes
Agency-Defined Phase III Clinical Trial?* ● No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

Funding Opportunity Number: PAR-13-128. Received Date: 2014-11-04T15:07:58.000-05:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ○ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

Specific Aims

Since 2003, resident physician duty hours have been regulated across the US in the interest of reducing resident fatigue and promoting patient safety. Continuous duty hours for first year trainees (interns) were restricted further in 2011. However, recent studies have associated the 2011 standards with less direct patient contact, increased medical errors, increased transitions of care, decreased educational opportunities, and only modestly increased sleep[3-5]. Program directors and trainees have expressed significant concern about the negative impact they perceive these rules have on patient safety and quality of training[6-8]. And so it seems that what was intended as a way to reduce error by managing resident fatigue is now felt by many to promote error through the compression of schedules and increased handoffs as well as decreased educational opportunities and professionalization required to produce independent physicians. No existing research helps navigate resident duty hour policy between these competing considerations. The goal of the iCOMPARE study is to fill these gaps. We will randomize internal medicine training programs to one of two duty hour schedules: the current standard (Current; Curr) or a Flexible schedule (Flex) and complete the following specific aims:

Specific Aim 1: Examine patient safety and costs under Curr and Flex duty hour schedules.
Specific Aim 2: Examine the quality of education under Curr and Flex duty hour schedules.
Specific Aim 3: Examine intern sleep time and alertness under Curr and Flex duty hour schedules.

iCOMPARE has one **primary hypothesis**:

H1a: *30-day patient mortality under Flex will not exceed (will not be inferior to) mortality under Curr.*

We will test related and complementary **secondary hypotheses**:

Patient safety and costs:

H1b: *7-day and 30-day hospital readmission rates under Flex will not exceed (will not be inferior to) the rates under Curr.*

H1c: *Complication rates, defined by selected AHRQ Patient Safety Indicators, under Flex will not exceed (will not be inferior to) complication rates under Curr.*

H1d: *The rate of prolonged length of stay under Flex will not exceed (will not be inferior to) the rate of prolonged length of stay under Curr.*

H1e: *Overall costs, as indicated by total Medicare payments, under Flex will not exceed (will not be inferior to) overall costs under Curr.*

Trainee education:

H2a: *Interns in Flex will spend greater time in direct patient care and education compared to interns in Curr.*

H2b: *Trainees in Flex will report greater satisfaction with their educational experience (greater ownership, greater continuity and lower burnout) than trainees in Curr.*

H2c: *Faculty in Flex will report greater satisfaction with their clinical teaching experiences and greater perceptions of safety, teamwork and supervision than faculty in Curr.*

H2d: *Standardized test scores for interns in Flex will not be less than (inferior to) those for interns in Curr.*

Intern sleep and alertness:

H3a: *Average daily sleep obtained by interns in Flex will not be less than (will not be inferior to) that of interns in Curr, as determined by a 14-day period of sleep monitoring using actigraphy and daily sleep diaries.*

H3b: *Interns in Flex will not have (will not be inferior to) greater average subjective sleepiness via KSS, or lower average behavioral alertness via PVT than interns in Curr, as determined by a 14-day period of morning sleepiness-alertness monitoring.*

Our primary outcome (30-day mortality) was chosen to ensure that any policy change in resident duty hours will not result in inferior patient safety. However, additional patient safety measures, as well as costs, education and fatigue management, are critically important considerations which our study addresses. Our study results will help the ACGME in its ongoing deliberations about optimal resident duty hour schedules. Changes in ACGME policies affect every teaching hospital in the United States, and as a consequence, every patient.

(a) Significance

United States policy limiting work hours in graduate medical education has become central to a highly charged debate surrounding the safety of patients cared for by resident physicians, the safety of resident physicians, the education and production of a future physician workforce, and the cost of patient care and of graduate medical education. While some scholarship addresses individual elements within this mix, essentially no existing work has examined their interplay or their balance. The debate often centers on the tension between evidence from human chronobiology and sleep research, which argues for shorter trainee shifts to prevent fatigue that can increase errors, and evidence from operations research, which argues for more continuity of care because patient handoffs lead to errors and reduce the effectiveness of education necessary to produce independent physicians. The balance between these competing concerns may affect patient safety, the cost of medical care, and how new physicians are professionalized into taking longitudinal responsibility for patients. At the request of Congress, the Institute of Medicine (IOM) charged the Committee on Optimizing Graduate Medical Resident Hours and Work Schedules to Improve Patient Safety to develop evidence-based strategies to balance these concerns. Dr. Dinges of our team served on that committee and Dr. Johns of our Advisory Board chaired it [9]. The 2009 IOM report identified the need to balance fatigue mitigation with continuity and education, and noted both the evidence gaps in the field as well as the estimated increase in health care costs of $1.7 billion annually that proposed duty hour restrictions would create.

In 2011, the Accreditation Council for Graduate Medical Education (ACGME) imposed more restrictive duty hour standards for all trainees. The new duty hours limited post-graduate year 1 (PGY1) trainees (also called interns) work to no more than 16h duty periods continuously. This change greatly increased the frequency of patient handoffs. Alternative work schedules have been proposed that combine extended shifts to maintain continuity of patient care with efforts to manage fatigue[10].Rigorous examination of the comparative effectiveness of these evidence-based approaches is essential to optimizing both current quality of care in America's teaching hospitals as well as the competency of our future physicians. **iCOMPARE (Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education) is designed to fill this unmet need for a high-quality, generalizable body of evidence to inform national duty hour policy.**

iCOMPARE is a cluster randomized trial of 58 Internal Medicine (IM) training programs to compare the current duty hour standards (**Curr** throughout this proposal) with a more flexible set of standards limited by three constraints (**Flex**): [1] work no more than 80 hours per week; [2] call no more frequent than every 3rd night; and [3] one day off in seven—all averaged over four weeks. This design is parallel to the FIRST trial—a duty hour trial for residents in general surgery conducted between July 2014-June 2015. Importantly, duty hour limits need to have an evidence base that is relevant to both primarily procedural and cognitive fields. Therefore, the iCOMPARE trial is a necessary analog to the surgical trial. The 58 IM programs in iCOMPARE provide care to patients in over 100 hospitals. The primary outcome selected for assessment focuses on patient safety because the fundamental justification for the restricted schedule was that it would improve patient safety. The iCOMPARE trial primary hypothesis-testing outcome will involve measurement of patient safety via 30-day mortality among Medicare beneficiaries. In addition, the trial will address two other areas of central policy and scholarly relevance: trainee education and trainee sleep and alertness. Education will be measured using standardized and validated assessments of individual residents, routinely conducted by the American College of Physicians (ACP), ACGME, and the Association of Program Directors in Internal Medicine (APDIM). These assessments are supplemented with tailored surveys and local time-motion measurements. Sleep and alertness will be measured electronically using standard 24h wrist actigraphy, sleep and sleepiness logs, and psychomotor vigilance testing (PVT) for alertness.

This project has direct clinical and policy relevance. If the central hypothesis of our proposal is supported, we expect that the ACGME will revisit the current duty hour standards and, informed by the results of this trial, extend the flexibility of intern duty hours in the direction of the Flex intervention arm. In the meantime, participating programs may experience reduced costs during the trial because extended resident work periods may lower costs required to support continuity of inpatient care delivery—a discrete hypothesis that will be tested. Rarely do individual studies have such an immediate connection to broad and important health care change. Such a change in policy will affect every teaching hospital in the United States, every patient at these hospitals, and every future patient cared for by the next generation of physicians.

An important note about this resubmission and the chronology of this study. Considerable preliminary work led to the iCOMPARE submission to NHLBI in February 2014. The investigative team had received financial support from Private Source to develop a proposal to study an evidenced-based approach to duty hours

relative to patient safety, intern education and sleep, that would be competitive for NIH funding to carry it to conclusion. In addition to the Private Source we engaged the community of Internal Medicine leadership organizations (American College of Physicians (ACP), American Board of Internal Medicine (ABIM), Alliance for Academic Internal Medicine (AAIM), and the Department of Veterans Affairs), as well as the community of Internal Medicine (IM) program directors. When our original proposal Priority Score was made available and we learned that it was unlikely to be funded, we faced a decision about whether we could field the study starting July 2015. We elected to substantially modify our NIH proposal in response to the reviewers' valuable comments and resubmit it. At the same time, we remained committed to moving forward with the study for a July 2015 start date. We had saved enough money from the initial Private Source to support a downscaled study even if NHLBI funding was not initially available. We felt it was essential to commit to conduct a downsized study with Private Source because we had a time-sensitive duty-hour waiver from the Private Source for a trial—one that could be lost if the start date was postponed. Moreover, the policy question was pressing and we had already engaged IM community interest to make such a trial possible.

We therefore constructed a revised plan for iCOMPARE that was both highly responsive to the study section review and also feasible with the limited resources we had available from Private Source. To make this plan possible with only Private Source, we had to eliminate many of the additional aims we felt were important, with the hope that they could be reconstituted in an NHLBI resubmission that was successful. The current proposal is an attempt at that reconstitution, informed by additonal data we have acquired since the first review.

Given these considerations, we plan to conduct the downsized iCOMPARE study, currently supported only by Private Source beginning with the July 2015 new residency cycle. 58 residency programs have submitted applications to be randomized by the time this NIH revised proposal is reviewed. That enrollment meets our statistical power requirements for the NIH revised application. If this proposal is successful, the timing of the NHLBI funding decision and the timing of the award are compatible with the timeline for the downsized iCOMPARE study.

We appreciate the obvious question, "Why should NHLBI fund this study if the investigators are going to do it anyway?" The iCOMPARE study that is supportable with the Private Source is a skeleton of what a transformational trial could and should be. The purpose of this NIH revised submission is to put substantial science behind our examination of physician training practices. While all reviews of trials face questions of feasibility, we are in the position of having demonstrated that we have already met our enrollment target. The current revised NIH proposal reflects a unique opportunity to build on an existing experimental process to inform the many more critical scientific questions yet unanswered about the training environment for future physicians. Our revised submitted budget reflects both the committed parts of the project (supported by Private Source and the requested parts to be funded by NHLBI. The policy decisions surrounding resident duty hours center primarily around the safety of current patients, but they affect intern education and sleep in ways that have potentially more enduring and subtler effects that also deserve consideration. Without NHLBI funding, we would be unable to evaluate many outcomes that could additionally inform future Private Source policy decisions regarding physician training.

(b) Innovation

iCOMPARE, and the companion FIRST trial among general surgery residents, are the most comprehensive prospective trials proposed to date to evaluate the impact of duty hour policy. This revised iCOMPARE trial will be the largest randomized clinical trial in internal medicine medical education ever conducted. It uses a combination of established and novel outcomes and assessments, in a cluster randomized design.

A consequence of recent duty hour policies has been the compression and fragmentation of residents' clinical experience during a work week that reduces their educational development and professionalization[3]. "Work compression" results as trainees have to complete similar work in shorter periods of time in the often under-resourced settings of current academic medical centers, and because the percentage of trainees' time in the hospital giving and accepting handoffs competes with time for face-to-face patient care and education. "Fragmentation of care" results as frequent handoffs introduce the opportunity for communication errors across faculty, patients and trainees. What was intended as a way to reduce error by managing resident fatigue is felt by others to promote error by compressing schedules and increasing handoffs. Furthermore, limited intern shifts require expanded coverage models that often utilize more trainees, faculty, or allied health professionals. These models are expensive (as noted, the 2009 IOM report[9] estimated cost increases of $1.7 billion annually), and can further compromise education because they exacerbate tensions between operational and educational goals of hospitals. To examine these effects, we will track patient outcomes and costs derived from

Medicare claims. Moreover, we will examine targeted educational outcomes. Few data exist describing the impact of duty hour standards on educational opportunities and outcomes, and most studies measuring educational outcomes lack contemporaneous control groups that allow for comparisons between groups of trainees on different duty hour schedules.[11-15]

Although the 2011 reduction in the duration of continuous time interns could be on duty was assumed to promote increased sleep, this work-hour restriction was an indirect and ultimately inefficient attempt to increase sleep time. Only moderate correlation has been oberved between resident work hours and sleep time[16,17]. We have now shown this more specifically in our study of >8,000 days of actigraphy and sleep-wake times on a total of over 300 IM interns, working within the Private Source defined duty hour limits during the years before and after the 2011 Private Source ule that limited continuous time at work to 16 hours. Remarkably, neither the 16h work limit nor a protected nocturnal nap sleep in the pre-2011 28h call cycle changed the mean daily total sleep time across the study weeks of intern training. Interns averaged just under 7h sleep per day on all schedules prior to and following the 2011 duty-hour changes. This finding also held comparing interns with and without protected nap periods. We believe these important new sleep findings suggest that duty hours within the range induced by the 2011 changes do not markedly change the average daily sleep obtained by IM PGY1 interns. Interns appear to normalize their work-schedule swings in daily total sleep time to a level just below 7h per day. Habitually averaging <7h sleep per day can result in a cumulative sleep debt over time that reduces alertness[18-20], especially during night and early morning periods[21,22]. However, in order to understand the spectrum of effects of changes in duty hour policies (mortality, costs, education, and sleep), our findings need to be confirmed in a more representative sample of interns with specific sleep measures including, most prominently, impaired alertness due to cumulative sleep debt. In addition, our findings need to be broadened in a larger study to highlight the use of and need for fatigue management strategies (e.g., increased sleep when possible, use of caffeine, exposure to light) to help protect against modest sleep debt.

The implementation of recent duty hour standards was intended to reduce resident fatigue and thereby increase resident and patient safety, but these rules have raised their own safety concerns associated with fragmented continuity, as well as educational concerns for the trainees who will become our independent physicians of the future. **iCOMPARE and the currently deployed FIRST trial are the first large-scale prospective randomized trials that help us navigate resident duty hour policy between these competing considerations.**

(c) Approach

We begin this section with a summary of our experience and capabilities as a Clinical Coordinating Center (CCC) with sections numbered to roughly correspond to the list of requested information in the *Experimental Approach* of the announcement (PAR-13-128).

1) CCC investigators' expertise and track record We have assembled a team of investigators with outstanding research and leadership experience in graduate medical education, sleep, and policy with a history of effective collaboration with each other and stakeholders relevant for dissemination and impact. The DCC includes investigators with similarly outstanding experience in the conduct and data analyses of multicenter trials. Those investigators, including James Tonascia, PhD, Jeffrey H. Silber, MD, PhD, and Dylan Small, PhD, are included in the parallel DCC application.

David A. Asch, MD, MBA is Professor at the Perelman School of Medicine (PSOM) and the Wharton School and Senior Fellow at the Leonard Davis Institute of Health Economics (LDI), all at the University of Pennsylvania (UPenn). He has had a 25-year career in health policy research and among his over 250 publications he is particularly well known for his policy research in graduate medical education. He wrote the first paper on resident duty hour limits to appear in the medical literature[23]. He served on the recent IOM Committee on the Governance and Financing of Graduate Medical Education[24]. He created and directed from 2001 to 2012 the Department of Veterans Affairs' national center to support vulnerable populations and reduce racial disparities. From 1998-2012 he directed UPenn's Leonard Davis Institute of Health Economics which, at over $125 million in annual research funding (mostly from NIH), became perhaps the largest university-based health policy research organization in the world. He has directed many multicenter trials funded by NIH and other federal funders. He has received numerous awards for his contributions to research, medical education, and policy and is an elected member of the Institute of Medicine (IOM).

Mathias Basner, MD, PhD, MSc is Assistant Professor of Sleep and Chronobiology in Psychiatry at PSOM. He is an epidemiologist who has published the first large-scale population-based studies from economic databases on the role of paid work hours on sleep. He has also performed seminal laboratory and field studies

on the effects of noise on sleep, and was the first author of a 2014 review on noise and health in *The Lancet*[25]. He was a co-investigator in the two VA-funded trials on protected sleep periods for interns, and he has spearheaded the acquisition of actigraphically acquired sleep data from interns under the duty hour prior to and following the 2011 changes institute by Private Source He is member of the Sleep Deprivation Steering Committee of the American Academy of Sleep Medicine and has served as the fatigue expert on a National Academy of Science committee on FAA air traffic control staffing levels.

David W. Bates, MD, MS is Chief of the Division of General Internal Medicine and Primary Care and Chief Clinical Innovation Officer and SVP at Brigham and Women's Hospital, and Professor of Medicine at Harvard Medical School. He is an internationally known expert in medication safety, patient safety, evaluation, and clinical informatics, and he has also done extensive work on improving efficiency, quality, and on assessing health information technology (HIT) adoption and issues around interoperability. He did some of the leading work demonstrating the effects of implementation of computerized physician order entry on medication safety. He has also published on the effects of sleep on errors and adverse events. He is an elected member of the Institute of Medicine and serves as external lead for patient safety research for the World Health Organization.

Lisa Bellini, MD is Professor of Medicine and Vice Dean for Faculty Affairs at PSOM and Vice Chair for Education in the Department of Medicine. She has served as Program Director of the Internal Medicine Residency since 1996, overseeing 154 residents and 150 subspecialty fellows. From 2005-2008 she was the Associate Dean for Graduate Medical Education and Designated Institutional Official for UPenn with responsibility for all 68 UPenn sponsored programs. Nationally, she has held several leadership positions in Alliance of Academic Internal Medicine (AAIM) and served on several key committees for the Accreditation Council for Graduate Medical Education (ACGME). She was a member of the IOM Committee on Conflict of Interest, which has had a major impact on professional conduct within the academic community. Her research focuses on medical education, including the health and well-being of residents and faculty as well as the effects of fatigue and sleep deprivation on patient outcomes and the learning environment.

Sanjay Desai, MD is the Director of the Osler Medical Training Program at the Johns Hopkins Hospital and Vice Chair of Education for the Department of Medicine. He is also an Associate Professor of Medicine in the Johns Hopkins School of Medicine. He oversees 140 medicine trainees and over 200 subspecialty fellows. He led the residency program at Hopkins through the most recent changes in duty hour policy. He has won numerous teaching awards and has published widely on graduate medical education topics, with a specific focus on duty hour regulations, including a seminal 2013 single site crossover design study suggesting that stricter duty hour rules increased sleep duration among residents, but decreased patient continuity, educational opportunities, and perceived quality of care[4].

David F. Dinges, PhD is Professor and Chief of the Division of Sleep and Chronobiology, Director of the Unit for Experimental Psychiatry, and Vice Chair for Faculty Affairs and Professional Development in the Department of Psychiatry at UPenn. He is a leading scientific expert on the neurobehavioral and biological need for sleep to maintain performance and safety, and countermeasures for the effects of sleep loss. Among his 250 publications are seminal studies on prophylactic napping, chronic sleep restriction, recovery sleep dose-response curves, recovery sleep dynamics, and phenotypic vulnerability to the effects of sleep loss. He developed the widely-used Psychomotor Vigilance Test (PVT) for detecting degree of sleep pressure. He has served on NRC and IOM reports on work hours and safety, including resident duty hours[9]. His research has been supported by NIH for 25 years, as well as by NASA, the Air Force Office of Scientific Research, Departments of Homeland Security and Transportation, and the Office of Naval Research. He has conducted field studies of sleep and performance in health care professionals[26,27], airline pilots and astronauts. He was awarded the NASA Distinguished Public Service Medal in 2007. He has served as President of the World Sleep Federation, and the (US) Sleep Research Society, and is the Editor-in-Chief of SLEEP, the leading international scientific journal on sleep research and sleep medicine.

Joel T. Katz, MD is the Director of the Internal Medicine Residency and Vice Chair for Education at Brigham and Women's Hospital. He is Associate Professor of Medicine at Harvard Medical School, where he holds the Marshall A. Wolf Chair in Medical Education. He has received numerous teaching awards, including the "Best Clinical Instructor at Harvard Medical School," which is voted on by the graduating class, five times. As an original member of the Harvard Work Hours, Health and Safety Group, he has contributed to research on the impact of duty-hour reform on health care provider physiology and patient safety[14,17,28]. Other areas of research focus include physician professionalism, physician burnout, curriculum innovation and novel training

experiences. He served on the leadership boards of the Association of Program Directors in Internal Medicine and the Massachusetts Medical Society Committee on Medical Education.

Peter Pronovost, MD, PhD is Director of the Armstrong Institute for Patient Safety and Quality at Johns Hopkins and Johns Hopkins Medicine's SVP for Patient Safety and Quality. Dr. Pronovost is well known for his simple but effective checklist protocol that virtually eliminated central line catheter infections. He has written over 400 articles and chapters related to patient safety and the measurement and evaluation of safety efforts. He advises the World Health Organization's World Alliance for Patient Safety. Dr. Pronovost has earned numerous awards, including the 2004 John Eisenberg Patient Safety Research Award and a MacArthur *Genius Grant* in 2008. He is an elected member of the Institute of Medicine.

Judy A. Shea, PhD is Professor of Medicine at PSOM where she is Interim Chief of the Division of General Internal Medicine, Associate Dean of Medical Education Research and Director of the Office of Evaluation and Assessment in the Academic Programs Office and a Senior Fellow at LDI. She is a national leader in medical education; in 2011 she was awarded the Society for General Internal Medicine (SGIM) Career Achievement in Medical Education Award and the John P. Hubbard Award from the National Board of Medical Examiners. Many of her more than 200 peer-reviewed publications focus on issues in medical education.. She was a key investigator in the VHA funded trial of a protected sleep period for medicine interns and a recent NHLBI study that included national surveys about duty hours to internal medicine and surgery trainees and program directors[10,15,26,29].

Kevin G. Volpp MD, PhD is Professor at PSOM and the Wharton School and Director of the LDI Center for Health Incentives and Behavioral Economics. He has done extensive research on the impact of duty hour reform on health outcomes[30,31]. He has published numerous articles about duty hour reform. He practices internal medicine at the Philadelphia VA Medical Center. He has directed many multicenter trials funded by NIH and other federal funders. He has received numerous awards for his contributions to research and policy and is an elected member of the Institute of Medicine.

Advisory Board: We also have an advisory board that will meet yearly to advise us on key issues related to design and dissemination. The board reflects experts in sleep, graduate medical education, and policy and includes ***Vineet Arora, MD, MA*** – Assistant Dean for Scholarship and Discovery at the University of Chicago and a national leader in medical education; ***Ruth Benca, MD, PhD*** – Professor and Vice Chair of Psychiatry at the University of Wisconsin and past President of the Sleep Research Society and the Associated Professional Sleep Societies; ***Karl Y Bilimoria, MD, MS*** - a surgical oncologist at Northwestern who is leading the FIRST trial on resident duty hours in surgical training; ***Patrick Conway, MD*** – Deputy Administrator of the Center for Medicare and Medicaid Services (CMS) and Director of the CMS Innovation Center in the US Department of Health and Human Services; ***Michael ME Johns, MD*** – Interim Executive Vice President for Health at the University of Michigan and Chair of the 2007-2008 IOM Committee on Resident Duty Hours.

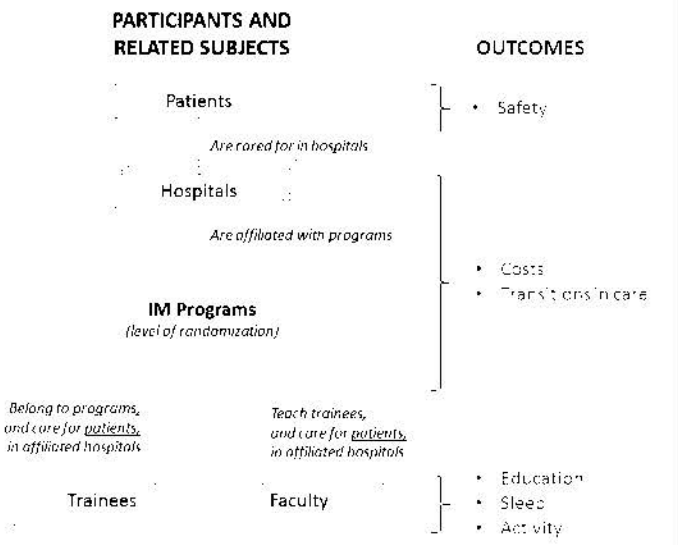
2) Background A 1971 study[32] that found fatigued interns tended to misinterpret electrocardiograms prompted discussion on duty hours, but no action. The death of Libby Zion[23] prompted the first state-level regulation of duty hours in 1989 in New York. Under increasing public and legislative pressure to restrict duty hours for graduate medical trainees, ACGME implemented duty hour standards for all accredited training programs effective July 1, 2003[33]. These standards represented one of the largest national efforts ever undertaken to reduce errors in teaching hospitals. The intent of these standards was to improve patient safety; however, the preponderance of data after their implementation, much of it produced by members of our team, demonstrated no definite benefit in safety, concerns for increased risks[30,31,34-38], and no clinically important improvements in Internal Medicine Board Scores subsequent to the 2003 reform[39]. Subsequently, and in response to a Congressional request, an IOM Committee was charged with making recommendations to optimize resident work hours to improve patient safety. In 2009, the IOM published its report recommending naps for any trainee working over 16h[7]. The ACGME then revised the national standards in 2011 mandating rest periods between duty periods, increased supervision for junior trainees, and a 16h limit on continuous duty hours for interns[40]. However, since the 2011 standards have been implemented, concerns have been raised regarding their impact on patient safety, trainee education, and health care costs. Studies have associated the new standards with less direct patient contact, increased medical errors, increased transitions of care, decreased educational opportunities, and only modestly increased sleep[3-5]. Furthermore, significant dissatisfaction has been reported by program directors and trainees about the negative impact on patient safety and quality of training[6-8].

One of the reasons ACGME limited continuous PGY1 work to 16h was to increase sleep time and thereby prevent fatigue-related errors. However limiting work hours to increase sleep time does not appear to have

been effective. As described above, our aggregate actiwatch + sleep diary data from 301 IM interns contributing >8,000 days reveals that their mean daily total sleep time is comparable across all duty-hour schedules that we have investigated prior to and following the 2011 limit of 16h. In agreement with this conclusion are data from single center RCTs in internal medicine that also suggest some alternative work-hour models may be equal or superior in relevant patient and trainee outcomes. One study randomized IM interns to a schedule with 16h limits or 30h limits[4]. During the window on which interns were on their longest shifts (a 48h period comprising either the 16h shift or the 30h shift), interns on the 16h schedule slept approximately 3 hours more than interns on the 30-hour schedule. However during a 4-week clinical rotation, interns on the 16h schedule did not sleep significantly more on average than interns on the 30h schedule. Additionally, transitions in care were 130-200% higher in the 16h schedule. **These data make a compelling case that the current policies might be improved to meet the complex and at times competing needs of the public.**

3) Design and rationale iCOMPARE will use a one-year randomized cluster design to compare two alternative work schedules for interns in 58 IM programs. The control schedule (**Curr**) reflects current duty hour standards. The intervention schedule (**Flex**) has three conditions: [1] work no more than 80 hours per week; [2] call no more frequent than every 3rd night; [3] one day off in seven—all averaged over four weeks. We will evaluate the differences between these alternatives in terms of patient safety, education, and sleep. We selected a more flexible set of rules for the intervention than in our original submission in response to input from the community of IM residency directors. Notably, this change in our intervention arm is now relevant for all PGY levels, not just the PGY-1 (interns) of our original submission. We are testing a more substantial intervention in this revision of the trial—more substantial in the flexibility it allows, and in the years it affects—and as a result, noninferiority will have even more policy meaning.

Figure 1: Nesting of patients, hospitals, and programs



Program selection and recruitment. Randomization is at the level of the IM training program (Figure 1). The ACGME has agreed to waive duty hour standards for participating programs randomized to Flex. As detailed in the companion DCC proposal, to obtain precise estimates of our patient safety outcome measures, programs included need to meet criteria for patient volume and program size (see *CCC Appendix 1* for CONSORT diagram). There are 379 IM training programs in the country. We exclude 119 programs reflecting the bottom 50% in resident-to-bed ratio and the bottom 25% in patient volume related to the diagnoses in which we will measure mortality in their affiliated hospitals. Within the 260 programs that remain, we exclude the 65 in the lowest quartile of program size to ensure we can feasibly obtain sufficient trainee measurements. The 195 remaining programs are eligible for inclusion. At this writing, we have recruited 58 of them and we intend to recruit more programs in part to further improve our statistical resolution and generalizability and in part because the incremental cost of including additional programs is very low.

Selected programs that agree to participate are estimated to have a mean of 30 interns and 50 PGY 2-3 trainees (residents). All of these trainees are eligible to participate in the education outcomes, as are the program directors in the enrolled programs. Programs assigned to the Flex arm will be asked to implement the flexibility in as many of their trainee rotations as possible. While programs assigned to Flex may vary in how much they implement their changes, which might suggest to some that the exposure is uneven in the intervention group, in fact iCOMPARE tests a *policy-level intervention*—answering the policy-relevant question: What happens if programs are allowed to relax some of the current duty hour conditions? This is akin to an intent to treat analysis of a drug in which adherence to the drug may vary across individuals. We will examine the degree to which programs randomized to Flex, change their rotations to make use of the flexibility; however, as in the FIRST trial, we do not specify hypotheses about this.

Many residency programs are affiliated with multiple hospitals. Hospitals affiliated with participating programs will be included for assessment of patient outcomes if they have sufficient program-specific trainee presence

and sufficient patient volumes (see *CCC Appendix 1* for CONSORT diagram). Eligible programs have been eager to participate in a study that is designed to influence national policy relevant to them and potential recognition in study publications (see *CCC Appendix 6* for sample information for program director recruitment). Although we had included financial incentives for program participation in our original proposal, we have found those incentives unnecessary, eliminating our need to cap the number of programs enrolled. All eligible programs may participate and, as noted, we have already met our minimum threshold for statistical needs.

Participating programs will be randomized to the Flex or Curr schedule between November and December of 2014. As a result, randomization will be largely complete by the time this proposal is reviewed at NIH. Education, safety and cost outcomes will be measured at all participating programs using comprehensive assessments from multiple approaches, leveraging presently collected data on individuals and programs by national organizations, including Medicare, ACGME, ACP and APDIM. Daily sleep will be assessed in a subset of the enrolled programs.

Retention, cooperation and follow-up plans. Our prior experience suggests that when program directors endorse an intervention, participation is high. In our sleep RCT intervention studies at UPenn and the Philadelphia VA, nearly 100% of the interns agreed to participate in the trials, and adhered to the request to wear wrist actiwatches and daily log into electronic recorders to quickly enter sleep and sleepiness information, and perform the PVT alertness test.[10,26]. Similarly, our team has broad experience with enlisting IM trainees and program directors in survey based studies[15,29,41-49]. Response rates are often above 80% when administered locally and approach 95% when collaborating with established organizations. While we have not budgeted incentives at the program level for most programs, we have done so for those programs participating in the more intensive parts of the study ($8,000 for sites involved in the sleep studies, and $3,000 for sites involved in the time motion studies). Participant-level incentives are described below.

4) Approach for each of the 3 Specific Aims and associated hypotheses

Specific Aim 1: Patient safety and costs outcomes *(hypotheses H1a-H1e)*

Policy changes to resident duty hours require confidence that current patients will be at no increased risk of harm. Although this study has multiple secondary hypotheses, Specific Aim 1 encompases our primary hypothesis. We compare Curr and Flex resident duty hour schedules in 30-day all location mortality. Secondary outcomes relating to safety include prolonged length of stay, 30-day readmission rate, complication rate, a new refined measure of patient deterioration (see DCC application), and resource utilization measures among fee for service Medicare beneficiaries with specific diagnoses. The approach and discussion for Specific Aim 1 are in the DCC application as this aim does not require direct data collection on patients by iCOMPARE. Patient outcome measures will be determined from Medicare claims data collected as part of routine clinical practice and administration, allowing us to efficiently and objectively collect and compare patient outcomes pooled across all randomized programs.

Specific Aim 2: Trainee education and process outcomes *(hypotheses H2a-H2d)*

Study population. Trainee education and process outcomes will be investigated three ways: time-motion measurements of the activities of trainees, surveys to trainees and program directors, and standardized test scores routinely collected by other organizations during the course of training. Given about 80 residents per program, we estimate that the study population of trainees across the 58 IM programs totals 4640.

Basis for education hypotheses. These hypotheses derive from three related concerns that short duty hour shifts: [1] reduce educationally rich continuity across the patient experience, particularly in the first 24 hours of hospital admission; [2] compress training time, thereby reducing direct patient contact for residents; [3] fragment training time by increasing handoffs, thereby reducing the sense of individual ownership of a patient's care leading to reduced morale, professionalization, and satisfaction. In the years since the implementation of the 2003 duty hours standards, a number of studies documented trainees' and program directors' reactions and perceptions to education, clinical care, and well-being. Views are mixed. Multiple studies report reduced burnout post 2003 duty hour reform[13,14], and improved quality of life[50,51], while other studies report burnout in the majority of residents, whether sampled after the 2003[52] or the 2011 policy[53] changes. Furthermore, there are common worries about decreased continuity of care[14,50], decrements in professionalism, fragmentation and less clinical experience and worse patient care due primarily to frequent handoffs[54,55]. A recent survey of nearly all IM trainees revealed that limited educational opportunities are the weakest part of the average inpatient rotation[15]. Program directors overwhelmingly agreed the 2011 duty hours regulations would likely negatively

affect the quality of the learning environment, workload, education opportunities, program administration, and patient outcomes[29]. Notably almost all of the research occurred prior to the 2011 duty hours changes.

Recruitment and retention. An important efficiency of this study is that many of the central measures we use are already collected as part of routine graduate medical education processes, are based on standardized and validated measurement principles, and have high data completion because they are required for program accreditation. We include some additional measures, both structured and timed to reduce burden and enhance complete data collection. We will also provide targeted financial incentives to programs and trainees to encourage responsiveness. The various incentives related to specific measures are detailed below.

Data collection schedule. Table 1 summarizes the key education and process outcomes along with the target and timing of the assessments

Table 1: Education Measures

Hypothesis	What?	Who?	When?	Why?	By Whom?
2a	Time-motion	PGY1	Jan-Feb 2016	Type of activities engaged in	CCC
2b	Just-in-Time surveys	PGY1 in target IM rotations	Random daily samples	Work intensity, ownership, continuity	CCC
2b	Satisfaction	PGY1-3	May 2015 (baseline) 2016	Attitudes	CCC
2b	Maslach Burnout Inventory	PGY1-3	May 2015 (baseline) 2016	Burnout	CCC
2b	ACGME year-end trainee survey	PGY1-3	May 2015 (baseline) 2016	Attitudes, perceptions of training	ACGME
2c	ACGME core faculty survey	Core faculty	May 2015 (baseline) 2016	Perceptions of safety, teamwork, supervision	ACGME
2c	PD satisfaction	PD	May 2015 (baseline) 2016	Clinical teaching satisfaction, costs	CCC
2c	PD Perceptions	PD	Fall 2015, 2016,	Morale, continuity, education, schedules	APDIM
2d	In-Training Examination	PGY1	Early PGY2 yr – 2015, 2016	Knowledge	ACP

CCC = NHLBI Clinical Coordinating Center; ACP = American College of Physicians; ACGME = Accreditation Council for Graduate Medical Education; APDIM = Association of Program Directors in Internal Medicine; PD = Program Director.

Hypothesis 2a. *Interns in Flex will spend greater time in direct patient care and education compared to interns in Curr.* Interns in a subset of 6 programs (3 each in Curr and Flex) will be recruited to measure their activities in the hospital. Participation will be voluntary and consent will be obtained as described in *Protection of Human Subjects*. We will select 10 interns at each site for observation. Observations will occur over 2-4 weeks mid-year (duration depends on availability of observers). As in our prior work, observers will be medical or nursing students on vacation or other nonscheduled blocks. Observers will be trained in the categorization of intern activities and will undergo quality control assessments. Handheld applications (e.g. iTouch) will be used to record time-in-motion assessments. This methodology has been used by our investigators recently in a multi-institutional study[3]. Observers will follow participating interns through a variety of shifts to quantify the amount of time they spend in various activities. Our primary outcome is time spent in direct patient care. Interns will be followed over the duration of their shifts; shifts will be sampled proportionate to the amount of time interns spend in them. Our goal is to observe 2-4 shifts per participating intern, varying the position in the call cycle and sampling both days and nights. Interns who participate in these observations will receive $50.

Hypothesis 2b. *Trainees in Flex will report greater satisfaction with their educational experience (greater ownership, greater continuity and lower burnout) than trainees in Curr.* This hypothesis is tested with several measures, some of which we have created for this study, but most of which are administered routinely. [1] We will use annual end-of-year surveys (EOY) to all trainees in the 58 participating programs. June 2015 surveys reflecting academic year 2014-2015 (the year before the intervention year) will serve as baseline data and the same instruments will be administered in June 2016–at the end of the intervention year. Key content will include domains addressing perceptions that we have assessed in prior national studies including perception of adequacy of independence, education opportunities, supervision, quality of care and safety[15,44] (draft survey in *Appendix 2.a*). We will also adapt questions from the survey to trainees developed by Dr. Shea of this team

for the FIRST trial (draft survey in *Appendix 2.b)*. [2] We will use the Maslach Burnout Inventory[56], a 22-item rating scale designed to assess three aspects of the burnout syndrome: emotional exhaustion (9 items), depersonalization (5 items), and lack of personal accomplishment (8 items). Items are answered on a frequency scale of 0 (never) to 6 (every day) (*Appendix 2.c*). [3] We will use the ACGME Resident Survey. Content includes the domains of faculty supervision and environment, evaluation, educational content resources, patient safety and teamwork (*Appendix 2.d*). ACGME has agreed to share these de-identified linkable data with us. Response rates are required to be above 70%. For all instruments we field ourselves, we will provide incentives at the program level. Trainees will receive $10 for completing the EOY survey. The six programs with the highest response rate will each receive $2,500.

During the intervention year, random samples of interns in target IM rotations will also receive brief surveys asking them to reflect on training experiences over the past 24 hours. The surveys (draft survey in *Appendix 2.e*) will be administered through a web-based application from UPenn. The content includes work intensity, number of and perceived quality of handoffs, ownership and continuity. On any given week day, an average of 15 interns will be on a targeted rotation within each of the 58 programs (15 x 58 = 870 interns, approximately 50% of all interns in the study overall). By random allocation, we will survey a 10% sample daily, or 87 interns. We will administer these questions by email accessible on a smart phone. The incentive for completing them will be lottery-based at the level of the program (since we want complete participation at a program level). Interns who complete the survey(s) will be entered into a lottery with a cash value of $25 every two weeks.

Hypotheses 2c. *Faculty in Flex will report greater satisfaction with their clinical teaching experiences and greater perceptions of safety, teamwork and supervision than faculty in Curr.* This hypothesis is tested with several approaches. [1] ACGME Core Faculty Survey. Annually the ACGME administers a survey to all core faculty in IM programs. Content mirrors the resident survey with domains of faculty supervision and teaching, educational content, resources, patient safety and teamwork. (see *Appendix 3.a* for 2012 survey items) The ACGME has agreed to share these data, de-identified at the level of the respondent, but identifiable at the level of the program. Response rates are required to be above 60% and are generally above 80%. [2] PD Satisfaction. We will develop and administer an annual survey to the 58 program directors of the participating programs. Consistent with our prior work in assessing program directors' perceptions of issues related to work-hours and education, the content will focus on the learning environment, educational opportunities, continuity of care, workload, patient outcomes, and program organization and administration[29]. This survey (draft survey in *Appendix 3.b*) will be administered via a web-based application housed at UPenn. [3] PD Perceptions. APDIM surveys all program directors every fall, with close to 100% participation. They have agreed to provide data relevant to this study, including perceptions of morale, continuity of care, attendance at conferences, burnout, existing nap opportunities and schedules, linking program identifiers to match participation in each arm of the study as well as the nonparticipating programs to help us assess generalizability. In addition, they have invited us to add 2-3 items relevant to this study to their survey. Drs. Shea and Bellini have successfully worked with the APDIM Survey Committee in the past to craft the survey content[29].

Hypothesis 2d. *Standardized test scores for interns in Flex will not be less than (inferior to) those for interns in Curr.* We will test this hypothesis with the In-Training Examination (ITE), an annual examination given each fall by the American College of Physicians (ACP). Most commonly, PGY2 trainees take the examination. The ITE includes 340 multiple choice questions, covering a broad domain of internal medicine. A single score is reported as a percentage of total questions answered correctly. The ACP has agreed to share these data with us. We will link scores at the level of the individual trainee with other assessments from other sources also performed at the level of the trainee (see *Letters of Support*).

Data management: See DCC application.

Quality control and performance monitoring: For the surveys administered locally, data acquisition will be monitored for completeness and quality. Each week a report will be generated that summarizes the overall response rates and provides counts of missing and any irregular (out of range) values. We will look at trends within each program and, if needed, work with local contacts to enhance response rates.

Statistical methods: The primary analyses will be unadjusted intent-to-treat analyses testing for differences between the intervention and control groups. The outcomes represent different types of data (means, percentages) and appropriate statistical tests will be selected. See the DCC application for details.

Safety and adverse event monitoring: All data collected for the educational outcomes will be kept on a secure server. Actual trainee identities will not be in the analytic file,reducing the risk that confidentiality can be breached. Reports will not be constructed on the program level when the n is < 10, as an additional protection

of confidentiality. All interns will be provided with training in handoffs before the start of the trial. See *Protection of Human Subjects* for further details.

Treatments effects monitoring: See DCC application.

Biases and challenges: Residents and faculty are used to completing surveys about various features of the training environment and trainees routinely take national assessments. Thus, using these data for research is unlikely to affect the quality of the observations. However, three potential biases remain: 1) Response bias. We have incorporated an incentive to mitigate the possibility of low response rates. 2) Hawthorne effect. People may behave differently when they know they being observed and this applies to the time-motion study. We will mitigate this concern by constructing a neutral explanation of what we are doing that does not reveal our hypotheses,and our main protection is observing over extended periods of time during which we expect any such effect will wane; 3) Social desirability. Trainees and program directors have strong feelings about work hour schedules. They could potential use the survey mechanism to voice and try to sway the conclusion or answer in a way they perceive is most valued. This concern has been noted by reviewers and we acknowledge it here and will do so in our interpretation and presentation of results.

Specific Aim 3: Intern sleep and fatigue management outcomes *(hypotheses H3a-H3b)*

Figure 2. Sleep-Wake Sample Summary

- 8 medium-large training programs
- 6 months per year × 1 year
- 5 interns per 14-day observation period per program
- Each intern contributes one 14-day observation period
- Half of the observations are in the Curr condition; half in the Flex condition
- Maximum observation is 6,720 days from 480 interns in each of the two schedules for 14 days each (maximum of 3,360 days from each of the two schedules)
- Expected observation (less 27% data attrition) is 2,452 days from 240 interns in each of the two schedules.

Study population. Interns training in 8 of the internal medicine programs enrolled in the trial (4 programs each in Curr and Flex) may volunteer to participate in a 14-day period of sleep-wake evaluation involving (1) continuous electronic wrist actigraphy recording of their sleep-wake times; and the following brief electronic responses (total time <4 minutes): (2a) onset and offset times of sleep periods in past 24h; (2b) rating of perceived sleepiness on the Karolinska Sleepinesss Scale (KSS); (2c) 3-min psychomotor vigilance (PVT) performance to asses behavioral alertness; (2d) number and duration of excessive sleepiness periods in past 24h. Interns from 8 medium to large training programs will be included in the sleep-wake evaluations to ensure programs can accommodate the need to complete 14-day sleep-wake data acquisition on an average of 10 interns per month (N=5 per 14-day period) for 6 months per year. Which months are used can vary by program to make data acquisition feasible for all programs in 1 year (June, July, and December will not be used due to high variation in activities and rotations and we use only 6 of the other 9 months in case there are other unique calendar challenges). This design allows us to collect 14-day sleep-wake data on N=80 interns per month (i.e., N=10 per site [N=5 per 14 days] × 8 sites), N=480 unique interns per year (over 6 months per site), each contributing a 14-day period. These participants and observations are distributed equally across each of the two arms, Curr and Flex. Maximum sleep-wake data could total 3,360 days from each schedule ([480 interns × 14 days each]/2 schedules = 3,360 days). In our previous randomized controlled trials of 5h and 3h protected sleep periods[10,26] from 6,768 days and 352 interns under the previous duty hour rules we obtained complete actigraph sleep-wake data (i.e., >23h per day) for 73% of days. Based on these results, in this study we anticipate collecting 2,452 days (i.e., 73% of 3,360 days) of sleep-wake data on N=240 interns undergoing each schedule over the 1-year period. Consequently, there will be adequate data to test sleep hypotheses.

Basis for sleep hypothesis H3a. *Average daily sleep obtained by interns in Flex will not be less than (will not be inferior to) that of interns in Curr, as determined by a 14-day period of sleep monitoring using actigraphy and daily sleep diaries.* We do not expect interns in the Flex condition to average less daily sleep compared to interns in the Curr schedule. This hypothesis derives from our extensive preliminary data, discussed above,revealing a consistent mean daily sleep duration of just under 7h for IM interns during the years before and after the more restrictive 2011 ACGME rule: [1] for pre-2011 duty-hour rules, which allowed extended work shifts, daily total sleep time (TST) = 6.938h (SD = 1.736h); [2] for post-2011 duty-hour rules, which limited work to 16h, TST = 6.946h (SD = 1.451h). Therefore, regardless of the duty hours, PGY1 mean daily sleep duration has remained the same, and we therefore expect that to be the case when comparing the Flex and Curr schedules in the proposed trial.

Basis for sleep hypothesis H3b. *Interns in Flex will not have (will not be inferior to) greater average subjective sleepiness via the well-validated Karolinska Sleepiness Scale (KSS)[57], or lower average behavioral alertness via PVT[21,22] than interns in Curr, as determined by a 14-day period of morning sleepiness-alertness monitoring.* Since mean daily sleep duration is expected to be the same in the Flex and Curr schedules, based on our extensive data acquired to date, and since both schedules can involve occassional night duty (estimated to be approximately 25% of consecutive work days), we expect no difference in morning subjective sleepiness (KSS) and objective behavioral alertness (PVT) between the two schedules. Although we expect no differences between conditions, we expect mornings after night shifts (Curr) and extended call (Flex) to involve greater sleepiness and reduced objective alertness than morning after a night of sleep, which we observed in our previous studies[10,26].

Recruitment and retention. Interns volunteering to have their sleep-wake monitored will be recruited by onsite project coordinators (with support from the CCC). They will be informed that their training program's agreement to be in the study does not obligate them to participate in the sleep monitoring portion of the study. Based on preliminary actigraphy data on sleep (6,768 days of data >23h) we acquired from N=352 interns in RCTs evaluating protected sleep periods, we retained >98% of the interns. Since the proposed trial involves half as many days of sleep monitoring, but involves more sites, we anticipate retention for the full 14 days of sleep monitoring to be ≥73%. To promote retention, project coordinators at each site will keep track of the schedules of interns being monitored for sleep, and ensure actigraphs are charged, programmed and correctly distributed to recruited interns for each 14-day monitoring period, and ensure that iPads are available for morning assessments and data downloads. They will communicate regularly with Dr. Dinges' laboratory to solve problems of subject retention and data acquisition. We will also provide financial incentives to programs participating in sleep measurements to promote recruitment and retention. Specifically, each intern completing ≥ 80% of the requested measurements during a 14d period will receive $50.

Data collection schedule. Interns will wear wrist actigraphs (Pulsar Informatics STAR watch) for 14 consecutive days. The STAR watch continuously records activity level, sleep timing, ambient light, and off-wrist periods. Each morning (8-9am) interns will complete the iPAD assessments related to the most recent sleep period (timing, disruptions), current sleepiness level (KSS scale), the number of excessive sleepiness episodes recalled in the past 24h, and perform the 3-minute PVT test of behavioral alertness. At the conclusion of each 14-day period, actigraphs will be recharged and reprogrammed by site coordinators for the next participants, using a Pulsar application on the iPad.

Data management and quality control. Raw data (from actigraphy and iPad) will be transmitted to a secure server at Dr. Dinges' laboratory for review and registration for adherence and quality control, blind to condition. Raw actigraphy data then will be transmitted to Pulsar for application of a sleep scoring software algorithm and extraction of sleep outcome variables (onset, offset, duration) and outcome variables from the iPad electronic scales and PVT performance. Pulsar will transmit the raw and processed actigraphy and iPad data back to Dr. Dinges' laboratory for independent evaluation and verification by technical staff regarding the accuracy of the actigraphy algorithm scoring, as well as the validity of the self-report sleep and sleepiness data, and the validity of interns' adherence to the PVT performance test. These data collection procedures have been successfully used by Dr.Dinges laboratory and Pulsar Informatics in a recent major remote monitoring study for National Space Biomedical Research Institute and NASA[58]. Approximately every 2 weeks, the extracted data on sleep and performance will be transmitted from Dr. Dinges' laboratory to the DCC for analysis and archiving via secure processes. See DCC application for additional details.

Performance monitoring. Site coordinators will be contacted weekly (more often when needed) by iCOMPARE investigators managing sleep measurements (there will be daily coordination between Dinges laboratory and Pulsar Informatics) regarding confirmation of actigraphs being worn by specified participants (coded ID numbers), transferal of equipment to next scheduled interns, equipment integrity, confirmation of data transmission, and all other issues relevant to sleep data acquisition and equipment integrity. Lost and damaged equipment will be replaced immediately. Transmission of actigraphy and iPad data will occur daily when interns complete iPad tests. This will include electronic time stamps of when data were entered on iPads by the intern (thus permitting identification of data entered at times other than the morning window (8-9am).

Statistical methods. See the DCC application.

Safety and adverse event monitoring. There was no evidence during our two previous randomized trials of internal medicine residents that the sleep-wake monitoring technologies affected behavior of the interns or others. All interns will complete training in fatigue management and those interns volunteering for sleep-wake

monitoring will also undergo informed consent procedures described in the *Protection of Human Subjects* attachment. Interns participating in sleep-wake monitoring will be permitted to remove the watch for bathing and any activity for which the watch could pose a risk (e.g., working on moving equipment).

Treatments effects monitoring. See the DCC application.

Biases and challenges. Actigraphy and iPad data on sleep and alertness will be evaluated for data integrity (i.e., missing data, mis-scored data, non-compliance to PVT requirements). Based on experience, corrections to mis-scored actigraphy data and PVT non-compliance data are expected to be less than 5% of data. A precise log of all data corrections made will be part of each data transmission to the DCC—organized to permit data analyses to be done with and without the corrected data included. The interns eligible for sleep monitoring will be recruited from the larger programs in our study to balance obtaining sufficient numbers of interns with the logistical complexities of adding programs. However, we have no reason to believe that larger programs would be systematically different from smaller programs in this regard.

Safety. Both acute and chronic sleep loss, as well as night duty, occur in all trainee schedules including Curr and Flex. Therefore, for safety, fatigue management strategies (e.g., increased sleep when possible, effective use of caffeine, reduced exposure to light wehn sleeping, and increased exposure when awake) will be provided to all enrollees in the trial to help protect against fatigure-related risks.

5) CCC internal organization, collaboration and communication The CCC will be staffed with a project director, supported by a project manager and research technicians as described in the budget justification, who will organize regular internal staff meetings and liaison group calls with the program sites, the sites engaged in the sleep assessments, and the sites engaged in the time motion assessments. These roles are described in the separate attachment *Study Organization and Administration*. Reports from these meetings will be provided for Steering Committee and Executive Committee meetings and will include detailed performance analyses, study status reports, and materials related to publication progress.

As a **pragmatic trial** many of the important outcome measures we need are collected automatically; nevertheless, this is a large trial with multiple aims and partners, and it will not work without effective collaboration and communication. As noted, monthly Steering Committee meetings and weekly Executive Committee meetings joining the CCC and DCC will form the organizational basis for our collaboration, supplemented by the liaisons with the program sites. The team will also communicate regularly using email and the iCOMPARE website. The use of this site as a hub for both internal and external communications is described in the DCC Research Strategy. We may also take advantage of project management software programs (e.g. Basecamp) that we have used for other large projects. The leadership proposed for the CCC and DCC have spent their careers in collaborative multicenter research. For example, Dr. Asch is currently leading a CMS-funded clinical trial that has recruited patients from 43 states so far and Dr. Tonascia (PI of the DCC) has led DCCs for many multicenter trials.

6) Summary We have defined a set of hypotheses that are required to make a fully informed decision regarding the future training of physicians. To this goal, we have developed a dissemination strategy to extend the reach of our findings beyond the scientific community and directly to leaders in government and health care organizations. If the primary hypothesis of the proposal is supported, we expect that the ACGME will extend the flexibility of intern duty hours in the direction of the intervention arm. Rarely do individual studies have such an immediate connection to broad and important health care change. Such a change in policy will affect every teaching hospital in the United States.

This study will also advance discovery more generally, providing new insights into the relationships among sleep, performance, education, and patient safety—all in the naturalized setting characteristic of pragmatic trials. We have assembled a team of investigators that includes many of the nation's leaders in the content areas of this project, and in the methods necessary to advance them. This team has a track record of taking complex projects to completion and doing so with rigor and impact.

Protection of Human Subjects

This Human Subjects Research meets the definition of a clinical trial.

1. Risks to Human Subjects

a. Human subjects involvement, characteristics and design

This proposal is a multi-center randomized trial with randomization at the level of the Internal Medicine (IM) program. The decision to enroll in iCOMPARE will be made by the IM program director and other leadership at the program; the residents and faculty in a program will follow the decision made by their governing person or group. Residents at an iCOMPARE program will follow the duty hour schedule assigned by iCOMPARE to their program; they will not have a choice about which duty hour schedule they follow. Residents and faculty will have a choice about participating in iCOMPARE surveys and substudies as detailed below. These approaches are consistent with routine operations of residency programs, in which program directors decide on program structure and shape schedules within existing regulations, and it would be impossible to have different duty hour schedules for different residents within a single program.

We estimate that 58 program directors, 580 faculty, and 4640 trainees will be involved. The trainees are 29.4 years old on average[1]. Participating programs must meet eligibility criteria related to presence in hospitals with sufficient Medicare patient volume, patient diagnoses, and resident-to-bed ratio and number of trainees; the eligibility criteria are designed to assure sufficient trainee presence and patient outcomes (see CCC Application, Appendix 01 - CONSORT diagram).

b. Sources of materials

Three groups of human subjects will provide data to iCOMPARE: trainees, program directors and faculty, and patients, which we discuss individually.

Trainees. Trainees participating in iCOMPARE include interns (PGY1), PGY2 and PGY3 trainees. Trainees providing data to iCOMPARE can be divided into two groups. Group 1 are trainees at the participating programs in May 2015 and Group 2 are trainees at the participating programs in July 2015 through June 2016.

In May 2015, *Group 1 trainees* will be asked to complete iCOMPARE assessments querying their attitudes, burnout, and mood/empathy. The surveys will be conducted via email to their IM program email address; the email will include a link to the survey. Participation will be encouraged, but voluntary, and tacit consent will be used for these surveys. Additionally, de-identified data from the ACGME end-of-year survey of Group 1 trainees (conducted in May 2015) will be provided by the ACGME to iCOMPARE. The ACP has agreed to provide iCOMPARE with de-identified In-Training Examination (ITE) scores for Group 1 interns.

Group 2 trainees will participate in iCOMPARE from June 2015 through June 2016. Group 2 trainees at participating programs will be given an introduction to the trial during orientation weeks in June 2015. These trainees will be asked to complete assessments querying their attitudes, burnout, and mood/empathy at the end of the intervention year. Additionally, Group 2 interns will be periodically surveyed about their educational and clinical experiences during the intervention year while on key study rotations as described in our proposal. All of these surveys will be emailed to the trainees' program email addresses; the email will include a link to the survey. Participation will be encouraged, but voluntary, and tacit consent will be used for these surveys. For some surveys, detailed in our proposal, we provide small financial incentives to encourage survey completion.

Additional information gathered from Group 2 interns includes the ACP In-Training Examination (ITE) and the ACGME end-of-year surveys, which will be provided by the ACP and ACGME. These data have both individual identifiers (e.g., a specific trainee) and program identifiers (e.g., the trainee is from the Internal Medicine Residency at the Hospital of the University of Pennsylvania). Upon receipt, all data provided with personal identifiers will be "anonymized" by a DCC biostatistician prior to use in analysis. Personal identifiers such as name will be stripped from the record and replaced with an identification number and participant code that will allow us to link ACGME surveys and ACP assessment scores at the level of the individual trainee, to other surveys developed by the iCOMPARE team. The result is that we will have, for each of the participating programs, a data set at the trainee level containing ITE test scores, ACGME survey responses, and iCOMPARE surveys that is de-identified at the level of the individual, but is identified at the level of the

program and year of training.

A Sleep and Alertness Substudy will be completed within a subset of 8 programs; volunteer interns at these 8 programs will have their sleep and alertness measured using actiwatches and iPads (for self-reported sleep times, subjective sleepiness ratings (Karolinska Sleepiness Scale [KSS]), and behavioral alertness via the 3-minute Psychomotor Vigilance Test (PVT)). Each intern participating in these measurements will be assessed for one 14-day period during the trial. We use only a subset of 8 programs for these outcomes because, statistically, we need fewer participants to test hypotheses related to sleep and alertness than we need to evaluate effects on patient mortality. Individual interns participating in the Sleep and Alertness Substudy will provide written consent to perform actigraphy and iPad assessments (i.e., sleep, sleepiness, and PVT performance). The draft consent form for the Sleep and Alertness Substudy is included in the CCC Application, Appendix 05 – Draft Consent Forms.

The intern volunteers participating in the Sleep and Alertness Substudy will be selected from interns on eligible rotations. We will explain to the interns in these programs in June before the academic year begins that during some months of the year a sample of interns on pre-specified rotations will be asked to provide 14-day periods of data while on the specified rotations. If in the sample, the intern will be given opportunities to ask questions prior to being asked to provide consent. We will emphasize that the choice to consent is their own and their decision will have no consequences in terms of training assignments or evaluations. They will be told that they are not responsible for equipment loss or damage. Interested and willing interns will be asked to provide written consent to participate in this portion of the study.

Research assistants at the Sleep and Alertness Substudy sites will issue the actiwatches with instructions for use and show interns how to use the iPad and complete the Psychomotor Vigilance Test (PVT). Interns will wear actiwatches (Pulsar Informatics STAR watch) for 14 consecutive days. Each morning (8-9am) interns will complete the iPad assessments related to the most recent sleep period (timing), sleepiness (KSS), and behavioral alertness (PVT. Actigraphy data will be automatically (wirelessly) downloaded from the STAR watch (all data since last download) to the iPad each time the intern completes the iPad assessments. Research assistants will confirm data downloads every day via communication with Dr. Dinges' laboratory and they will be available to meet with participating interns to resolve problems (e.g., replace a lost actigraph), to confirm proper use of the equipment and resolve any problems. At the end of the measurement periods the research assistants will meet with each intern to collect the actigraph and iPad. We have used similar procedures in our randomized trials of protected sleep periods under the previous duty hours[2] and had excellent adherence to these procedures.

A Time and Motion Substudy will be completed within a subset of 6 programs; volunteer interns will have their activity monitored using time-motion measurements. Interns participating in the Time and Motion Substudy will provide written consent to permit observers to follow them for a subset of their work periods for time in motion assessments. The draft consent form for the Time and Motion Substudy is included in the CCC Application, Appendix 05 – Draft Consent Forms.

The interns participating in the Time and Motion Substudy will be selected from interns on eligible rotations. Eligibility of rotations is determined using pre-specified criteria designed to ensure we sample sufficient rotations with a range of activities to meet statistical needs. We will explain to the interns in these programs in June before the academic year begins that during some months of the year a sample of interns on pre-specified rotations will be asked to consent to being observed during their work on the rotation. Before obtaining consent, interns will be given opportunities to ask questions and will be informed that they may ask for the observation to stop at any time—or to pause if for any reason more personal privacy is desired. Participation will be voluntary and written consent will be obtained. We will enroll 10 interns at each of 6 sites for observation. Observations will occur over a 2-4 week period mid-year (duration depends on availability of observers). As in our prior work, observers will be medical students or nursing students on vacation or other nonscheduled blocks. Observers will be trained in the categorization of intern activities and will undergo quality control assessments. Handheld applications (e.g., iTouch) will be used to record time-in-motion assessments. This methodology has been used by our investigators recently in a multi-institutional study[3]. Observers will follow participating interns through a variety of shifts to quantify the amount of time they spend in various activities. Our primary outcome is time spent in direct patient care. Interns will be followed over the duration of their shifts; shifts will be sampled proportionate to the amount of time interns

spend in them. Our goal is to observe 2-4 shifts per participating intern, varying the position in the call cycle and sampling both days and nights.

The immediate benefits of iCOMPARE for resident participants are minimal. Potential risks are described below. Overall the risk benefit ratio is favorable given the long term potential of this study to significantly contribute to our knowledge of the impact of duty hour rules on sleep, performance, education, and patient outcomes. All trainees in participating programs will be included in some level of data collection; thus, women and minorities will be included according to their representation in these populations. All trainees are over the age of 18.

Program Directors and Faculty. Program director and faculty perceptions and satisfaction surveys will be administered by iCOMPARE, the ACGME, and APDIM. For iCOMPARE surveys, participation will be encouraged, but voluntary, and tacit consent will be used as is typical for written survey materials of zero to low content sensitivity. iCOMPARE will survey program directors twice, once in May 2015 and a second time in May 2016. The ACGME end-of-year faculty surveys are completed annually among a subset of each program's faculty designated as core to the educational program. The ACGME has agreed to provide the May 2015 and May 2016 data to iCOMPARE, aggregated at the program level, not individually. We will not consent faculty at sites for use of these de-identified, aggregated data. The APDIM Program Directors survey is completed annually by program directors. APDIM has agreed to provide the Fall 2015 and Fall 2016 data to iCOMPARE. We will not consent program directors for use of their APDIM data. Data from all surveyed faculty will be included, thus, women and minorities will be included according to their representation in these populations. All faculty are over the age of 18.

Patients. Patient data will be limited to Medicare claims data obtained through the ResDAC program at the University of Minnesota[4]. All requests for Medicare claims data are made through ResDAC; there will be no direct data collection by iCOMPARE from patients. Waiver of patient informed consent and HIPAA consent will be requested, for three reasons. First, since the trial will involve thousands of patients, it would not be feasible to consent patients. Second, the risk to patients from participation is minimal—earlier retrospective analyses conducted by members of the current team demonstrated no difference in patient outcomes with even longer duty shifts than those tested in iCOMPARE[5,6]. Third, the data are not collected directly from patients; all patient data will be obtained from Medicare claims, requiring no active involvement by the patient. Patient care data will be eligible for inclusion regardless of patients' gender or race. Children are not included since they are unlikely to be Medicare beneficiaries and unlikely to be on internal medicine services, but we will, in addition, restrict analyses to those patients over the age of 65 because this group reflects the majority of Medicare beneficiaries.

c. Potential risks

The greatest risk to participants is the risk to confidentiality. In general, trainees' educational assessment scores will be individually de-identified and so should present little to no risk to confidentiality. All interns will receive Fatigue Risk Management Training (FRMT), as described below. All program directors will communicate to their trainees that participation (or lack of participation) in the iCOMPARE surveys and substudies will have zero effect on their trainee assignments or evaluations. Additionally, program directors will not know the survey completion rates or responses of individual trainees. For faculty, no information is collected that is individually identifiable. For patients, we use Medicare claims data to analyze clinical outcomes. Analysis of these administrative data, which are routinely collected, is felt to be the least intrusive method of measuring these outcomes and, given high standards of information security described below, also the most secure.

2. Adequacy of protection against risks

a. Recruitment and informed consent

Recruitment and consent for this study consists largely of enrollment of Internal Medicine Residency programs. There is no specific recruitment required for patients or for faculty. There will be recruitment and consent of individual trainees within selected programs participating in the Sleep and Alertness Substudy and the Time and Motion Substudy, and those processes are described above, under "sources of materials."

b. Protections against risk

IRB review: The University of Pennsylvania IRB has agreed to be the IRB of record for all of the enrolled programs and the DCC. Individual Internal Medicine training programs may choose to use the Penn IRB

for that purpose and we expect that most will. However, if individual sites prefer to use their own IRB, we will support that process with templated forms and materials. This study protocol, and our approaches to human subjects in general, has been reviewed and deemed acceptable by Dr. Emma Meagher, Chair of the University of Pennsylvania's Human Subjects Committee and Associate Vice Provost for Research, and also by other members of the human subjects committee.

Fatigue management: The iCOMPARE trial will evaluate two duty-hour schedules denoted Flex and Curr. The Flex schedule imposes minimal requirements on average shift lengths and frequency, and the Curr schedule represents the current ACGME-required schedule. Both duty hour schedules are fully described in the research strategy. In a subset of interns, we will determine how well each schedule relates to sleep, duration, subjective sleepiness and behavioral alertness, and in all interns we will determine the effects of duty hour schedule on high-quality patient care and trainee education. Since both Flex and Curr schedules involve night work and some sleep loss, the trial will also include fatigue risk management training (FRMT) for interns to mitigate fatigue risks inherent in both schedules, prior to beginning their internships. To mitigate risks of fatigue, all interns will receive structured education in sleep deprivation and fatigue management in June 2015. FRMT will be made available to all interns in the participating IM program, and focuses on the use of scientifically-based fatigue countermeasures in three areas: (1) the use of prophylactic napping to reduce fatigue risk when working at night, and to extend recovery sleep time after a work period[7,8,9,10,11]; (2) the use of caffeine, bright light, and face-washing to mitigate the adverse cognitive effects of sleep inertia after any sleep period[2,13,14]; and (3) ways to prevent, identify and counter driving drowsy when transiting to/from work[15]. FRMT will be delivered via a web-based e-learning module developed by Pulsar Informatics, and will include assessment questions to ascertain whether the material is understood. Each intern at each participating program will complete the FRMT module before starting their training and results will be available to the Program Directors.

Procedures to ensure confidentiality: As described above, the greatest risk to participants is the risk to confidentiality. Individually identifiable information will be available only for the patients who are Medicare beneficiaries and for the subset of interns participating in the sleep and time-motion substudies. Those interns will be assigned an identification number that will be linked with the sleep monitoring data and PVT, time-motion measures, test scores (if individual collected), and surveys. Individual-level data for both trainees and patients will be kept confidential and stored only on the highly secure servers available for patient-level data at DCC sites (Johns Hopkins and the Children's Hospital of Philadelphia). No data will be stored on PCs or laptops. Only authorized project personnel will have access to the data as overseen by the DCC. All sensitive data will be encrypted using products employing AES-256 standards (or stronger). All data will be reported at units of aggregation which make impossible the identification of individual patients, residents, faculty, or program directors.

3. Potential benefits of the proposed research to human subjects and others

There are no substantial direct benefits to research participation other than contributing to the development of new knowledge as described below. However, risks are also low and managed. If the hypotheses are supported, the policy changes that are expected to result will be of benefit to patients, faculty, and trainees, as described below, under "importance of the knowledge to be gained."

4. Importance of the knowledge to be gained

This study has immediate policy relevance because it compares, in a highly naturalized setting, sleep, education, and safety outcomes of potential duty hour reform. The implementation of these standards has raised safety concerns associated with fragmented continuity and increased patient handoffs between physicians, as well as educational concerns for trainees, given the same loss of continuity and the compressed time for learning and direct patient care. Because physician training affects not only the care of patients in teaching hospitals today, but also the care of all of the future patients of the graduating trainees as they move into independent practice, training policy has a potentially highly leveraged and enduring impact on health care quality.

5. Data and Safety Monitoring Plan

Who will manage and conduct the monitoring?

iCOMPARE data and safety will be monitored by the Steering Committee and by an independent Data and

Safety Monitoring Board (DSMB) as required by NIH guidelines for multicenter trials. The Steering Committee will monitor accumulating safety and performance data. The DSMB will also monitor accumulating safety and performance data. Because the intervention phase will be over before patient safety and costs outcome data are available, the DSMB will not be able to monitor the treatment effects on the primary outcome. Many of the education outcomes also will not be available until completion of the intervention phase which also further limits the DSMB's ability to monitor treatment effects. However the DSMB may monitor performance data and adverse events experienced by trainees. We expect the DSMB to be a multidisciplinary group with a written charge, with members appointed by NHLBI. The DSMB will be advisory to the NHLBI. We expect the NHLBI will provide investigators with a summary report after each DSMB meeting, with recommendations for the trial. Each site investigator will forward these recommendations to their site's IRB of record for the trial; the University of Pennsylvania IRB has agreed to function as a central IRB for the trial and sites may choose to use the central IRB or their own institutional IRB.

What will be monitored?

Internal monitoring of data and safety. The Steering Committee will monitor accumulating safety and performance data at regularly scheduled intervals to help assure participant safety and for quality assurance. During the implementation stage of the trial, the Steering Committee will monitor the 1) timeline and progress of refinement of the protocol and other study documents, data collection forms development, database development; 2) attainment of IRB approval at each participating site; 3) enrollment of programs; 4) and training and certification of study staff. As data collection begins, the Steering Committee will begin to monitor progress of 1) harvesting data from Pulsar on the intern sleep measures and ACGME and ACP for education measures; 2) completion of surveys of intensity, attitudes, time in motion, etc., by interns and faculty; 3) data requests and receipts from CMS; and 4) reports of safety concerns for trainees, faculty or patients that are possibly or definitely related to iCOMPARE. Reports of safety concerns may be received by the CCC or DCC directly from site staff or as noted by investigators upon review of performance data reports; reports of concerns will be reviewed by the CCC and DCC directors upon receipt and will be reviewed by the Steering Committee in a timely fashion.

DSMB monitoring of safety and performance data. Because the NIH grant will not start until 01 July 2015, the date the interventions start, the DSMB will not be able to review the protocol for the iCOMPARE trial before the interventions begin. Once the trial starts, the DSMB will monitor the accumulating performance data to ensure trainee safety and to review education and sleep outcomes acquisition and quality. Reports may include data tables, graphs, and figures and will include the most recent data available at the time the report was prepared or analyses completed (see DCC Application, Appendix 04 – Sample DSMB Report Table of Contents for the table of contents of a DSMB data report prepared by the DCC for another trial).

The DCC will be responsible for preparing reports for the DSMB to review. While data collection is ongoing, the DSMB report will include information on data quality and performance (e.g., survey return rates, completeness of data acquired from outside sources, protocol deviations) by site and treatment group. The actigraphy data on sleep/wake time, sleep disruptions and intern survey data on alertness, fatigue-related accidents, near misses, work intensity, mood, and time-motion, and trainee and faculty survey data on satisfaction will be accumulating on a continuous basis during the trial and will be included in each DSMB report as available. The education data from ACGME and ACP will be included as available. The patient safety outcomes (mortality, length of stay, complications, readmissions) are generated from CMS data, and each calendar year of claims data is generally available 9 months after the end of the relevant calendar year. Because of this delay, no report to the DSMB during the intervention phase will contain data on the patient safety outcomes from CMS (see more details on timing of reports below).

The DCC can prepare masked or unmasked reports for the DSMB. The DSMB charter will include information on the masking of the reports. Identification and circulation of external evidence (e.g. from other trials/systematic reviews) will be the responsibility of the director of the CCC and will be presented to the DSMB if applicable. One charge to the Advisory Board assembled for this project is to assist in the identification of external evidence. Any DSMB member may also bring pertinent information to a DSMB meeting.

Proposed monitoring time points

The DSMB will meet after the end of the intervention (i.e., after June 30, 2016) to review available sleep, education, and performance data. The Medicare data for the first six months of the intervention year (7/1/2015 –12/31/2015) are expected to be initially released by CMS in the Fall of 2016 (final release is expected in January 2017). A DSMB meeting could be planned for December 2016 or January 2017 during which the DSMB could get a preliminary look at the primary outcome results. The Medicare data for the 2nd six months of the intervention year (1/1/2016-6/30/2016) are expected to be initially released by CMS in the Fall of 2017.

Although we do not expect to have a formal interim look due to design and data delay issues discussed above, the DSMB (in conjunction with the NHLBI and iCOMPARE investigators) will make the ultimate decision about interim looks and the decision will be documented in the charter.

Where will the monitoring occur?

The DCC will be responsible for the production of the reports for review by the Steering Committee and DSMB. The reports reviewed by the Steering Committee will include performance data and safety data by site or event (not by treatment group), but will not include treatment effects data. The contents of the DSMB reports will be developed with the input of the DSMB members, NHLBI representatives, and DCC. The report will be sent to DSMB members at least one week before any meetings. The DSMB charter will document the meeting organization and DSMB voting rules. We expect the DSMB meetings will be a mix of in person and conference call meetings, depending on the content to be covered; the DSMB will decide the mode for each meeting.

How will reportable events be managed and reported?

The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head. In iCOMPARE, unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants will be reported to the University of Pennsylvania IRB (CCC IRB and the IRB of record for programs) and the Johns Hopkins IRB (DCC IRB) and the NHLBI within the required timelines (1 week of learning of event for serious adverse events and 2 weeks for other unanticipated events). Other institutions will report to their IRBs if not using the study IRB of record. Unanticipated problems in iCOMPARE might include summary reports that suggest that intern fatigue-related accidents, near misses or injuries or patient mortality differences are greater than expected; breaches of protocol in duty hour scheduling that result in trainees working more than the intervention schedules dictate; or breaches of intern or patient confidentiality.

How will sites/centers, and participating facilities (labs, pharmacies) be monitored?

The DCC will prepare performance reports to present to the Steering Committee at regular intervals. The reports will include data by program on IRB approvals, training and certifications, intern recruitment for actigraphy (where applicable), completion rates for surveys, missing data rates, compliance with the duty hours schedules and other protocol deviations, and resolution of data quality queries. Program level reports will be generated monthly and distributed to study investigators, program directors and chief residents. A sample performance report prepared by the DCC for another study that can be adapted for iCOMPARE is shown in the DCC Application, Appendix 06 – Sample Performance Report.

6. Clinicaltrials.gov registration

iCOMPARE is registered in clinicaltrials.gov (http://clinicaltrials.gov/ct2/show/NCT02274818 . The protocol registered is the protocol supported by the ACGME funding; the protocol will be updated to include the expansions allowed by NIH funding, if the NIH grant application is funded.

REFERENCES

1 https://www.acgme.org/acgmeweb/Portals/0/PFAssets/PublicationsBooks/2011-012_ACGME_DATABOOK_DOCUMENT_Final.pdf

2 Volpp KG, Shea JA, Small DS, Basner M, Zhu J, Norton L, Ecker A, Novak C, Bellini LM, Dine CJ, Mollicone, DJ, Dinges DF. Effect of a protected sleep period on hours slept during extended overnight in-

hospital duty hours among medical interns. JAMA. 2012;308(21):2208-2217.

3 Block L, Habicht R, Wu AW, Desai SV, Wang K, Silva KN, Niessen T, Oliver N, Feldman L. In the Wake of the 2003 and 2011 Duty Hours Regulations, How Do Internal Medicine Interns Spend Their Time? J Gen Intern Med. 2013 Aug; 28(8):1042-7.

4 http://www.resdac.org/

5 Volpp KG, Rosen AK, Rosenbaum PR, Romano PS, Even-Shoshan O, Wang Y, Bellini L, Behringer T, Silber JH. Mortality Among Hospitalized Medicare Beneficiaries in the First 2 Years Following ACGME Resident Duty Hour Reform. JAMA. 2007;298(9):975-983.

6 Volpp KG, Rosen AK, Rosenbaum PR, Romano PS, Even-Shoshan O, Canamucio A, Bellini L, Behringer T, Silber JH. Mortality Among Patients in VA Hospitals in the First 2 Years Following ACGME Resident Duty Hour Reform. JAMA. 2007;298(9):984-992.

7 Dinges DF, Orne MT, Orne EC, Whitehouse WG. Napping to sustain performance and mood: Effects of circadian phase and sleep loss. Night and Shiftwork. 3:23-30, 1986.

8 Dinges DF, Whitehouse WG, Orne EC, Orne MT. The benefits of a nap during prolonged work and wakefulness. Work and Stress 2:139-153, 1988.

9 Dinges, D.F., Broughton, R.J. (Eds.): Sleep and Alertness: Chronobiological, Behavioral and Medical Aspects of Napping. Raven Press, New York, NY, 1989.

10 Arora V, Dunphy C, Chang VY, Ahmad F, Humphrey HJ, Meltzer D.. The effects of on-duty napping on intern sleep time and fatigue. Annals Int Med. 2006; 144(11):792-798.

11 Roach GD, Darwent D, Sletten TL, Dawson D. Long-haul pilots use in-flight napping as a countermeasure to fatigue. Applied Ergonomics. 2011; 42;214e218.

12 Van Dongen,HPA, Price NJ, Mullington JM, Szuba MP, Kapoor SC, Dinges DF. Caffeine eliminates psychomotor vigilance deficits from sleep inertia. SLEEP. 2001;24 (7):813-819.

13 Hayashi M, Masuda A, Hori T. The alerting effects of caffeine, bright light and face washing after a short daytime nap. Clinical Neurophysiol. 2003; 114 ;2268-2278.

14 Santhi N, Groeger JA, Archer SN, Gimenez M, Schlangen LJ, Dijk DJ. Morning sleep inertia in alertness and performance: effect of cognitive domain white light conditions. PLoS One. 2013; 8(11):e79688, doi:10.1371/journalpone 0079688.

15 Dinges DF, Abe T. Transportation safety and operator sleepiness: where biology needs technology. Proceedings of the International Association of Traffic and Safety Sciences (IATSS). 2013; p. 88-120.

16 Reboussin DM, DeMets DL, Kim KM, LanKK. Computations for group sequential boundaries using the Lan- DeMets spending function method. Control Clin Trials. 2000;21:190-207.

Inclusion of women and minorities

Planned distribution of subjects by gender, race and ethnicity. We are recruiting internal medicine training programs and have estimated the gender/race/ethnicity of the interns participating in those programs based on the gender/race/ethnicity distribution of interns in prior years. We expect a similar distribution in this trial. There will be no selection of programs by gender or race or ethnicity.

We expect iCOMPARE to include women and minorities in all aspects of data collection without regard to gender or race or ethnicity – the trainees who experience the duty hour schedules, participate in the sleep and time-motion substudies, the faculty and program directors who provide data for the education outcomes, and the patients assessed for safety outcomes.

There is no evidence from prior studies that there will be any difference of effect of duty hour schedule by gender, race, or ethnicity.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: iCOMPARE - CCC - Lead Application

Domestic/Foreign: Domestic

Comments: time-motion substudy interns: 10 in each of 6 programs Estimated from https://www.acgme.org/acgmeweb/Portals/0/PFAssets/PublicationsBOoks/2011-2012_ACGME_DATABOOK_DOCUMENT_Final.pdf, which combines Asian and Pacific Islander and has Other instead of More than 1 race; Other category was assumed to be More than 1 race Ethnic Categories

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	9	12	1	1	**23**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	2	0	0	**4**
White	11	13	1	1	**26**
More than One Race	3	4	0	0	**7**
Total	**25**	**31**	**2**	**2**	**60**

Study 3 of 3

Funding Opportunity Number: PAR-13-128. Received Date: 2014-11-04T15:07:58.000-05:00

Inclusion of Children

Children will be excluded from iCOMPARE. Children are not members of any of the groups providing data to iCOMPARE (interns, PGY2 and PGY3 trainees, faculty, program directors, Medicare beneficiaries over age 65) and they are not the entity being randomized.

Literature Cited

1. Barger LK, Cade BE, Ayas NT, et al. Extended work shifts and the risk of motor vehicle crashes among interns. *N Engl J Med.* Jan 13 2005;352(2):125-134.
2. Ayas NT, Barger LK, Cade BE, et al. Extended work duration and the risk of self-reported percutaneous injuries in interns. *JAMA.* Sep 6 2006;296(9):1055-1062.
3. Block L, Habicht R, Wu AW, et al. In the wake of the 2003 and 2011 duty hours regulations, how do internal medicine interns spend their time? *J Gen Intern Med.* Aug 2013;28(8):1042-1047.
4. Desai SV, Feldman L, Brown L, et al. Effect of the 2011 vs 2003 duty hour regulation-compliant models on sleep duration, trainee education, and continuity of patient care among internal medicine house staff: a randomized trial. *JAMA Intern Med.* Apr 22 2013;173(8):649-655.
5. Sen S, Kranzler HR, Didwania AK, et al. Effects of the 2011 duty hour reforms on interns and their patients: a prospective longitudinal cohort study. *JAMA Intern Med.* Apr 22 2013;173(8):657-662; discussion 663.
6. Drolet BC, Christopher DA, Fischer SA. Residents' response to duty-hour regulations--a follow-up national survey. *N Engl J Med.* Jun 14 2012;366(24):e35.
7. Drolet BC, Khokhar MT, Fischer SA. The 2011 duty-hour requirements--a survey of residency program directors. *N Engl J Med.* Feb 21 2013;368(8):694-697.
8. Drolet BC, Spalluto LB, Fischer SA. Residents' perspectives on ACGME regulation of supervision and duty hours--a national survey. *N Engl J Med.* Dec 2 2010;363(23):e34.
9. Wolman DM, Johns MM, Ulmer C. *Resident Duty Hours:: Enhancing Sleep, Supervision, and Safety*: National Academies Press; 2009.
10. Shea JA, Dinges DF, Small DS, et al. A randomized trial of a three-hour protected nap period in a medicine training program: sleep, alertness, and patient outcomes. *Acad Med.* Mar 2014;89(3):452-459.
11. Eckleberry-Hunt J, Lick D, Boura J, et al. An exploratory study of resident burnout and wellness. *Acad Med.* Feb 2009;84(2):269-277.
12. Fletcher KE, Underwood W, 3rd, Davis SQ, Mangrulkar RS, McMahon LF, Jr., Saint S. Effects of work hour reduction on residents' lives: a systematic review. *JAMA.* Sep 7 2005;294(9):1088-1100.
13. Gopal R, Glasheen JJ, Miyoshi TJ, Prochazka AV. Burnout and internal medicine resident work-hour restrictions. *Arch Intern Med.* Dec 12-26 2005;165(22):2595-2600.
14. Myers JS, Bellini LM, Morris JB, et al. Internal medicine and general surgery residents' attitudes about the ACGME duty hours regulations: a multicenter study. *Acad Med.* Dec 2006;81(12):1052-1058.
15. Shea JA, Weissman A, McKinney S, Silber JH, Volpp KG. Internal medicine trainees' views of training adequacy and duty hours restrictions in 2009. *Acad Med.* Jul 2012;87(7):889-894.
16. Baldwin DC, Jr., Daugherty SR, Tsai R, Scotti MJ, Jr. A national survey of residents' self-reported work hours: thinking beyond specialty. *Acad Med.* Nov 2003;78(11):1154-1163.
17. Lockley SW, Cronin JW, Evans EE, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med.* Oct 28 2004;351(18):1829-1837.
18. Belenky G, Wesensten NJ, Thorne DR, et al. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res.* Mar 2003;12(1):1-12.
19. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep.* Mar 15 2003;26(2):117-126.
20. Mollicone DJ, Van Dongen HP, Rogers NL, Dinges DF. Response Surface Mapping of Neurobehavioral Performance: Testing the Feasibility of Split Sleep Schedules for Space Operations. *Acta Astronaut.* 2008;63(7-10):833-840.
21. Cohen DA, Wang W, Wyatt JK, et al. Uncovering residual effects of chronic sleep loss on human performance. *Sci Transl Med.* Jan 13 2010;2(14):14ra13.
22. Mollicone DJ, Van Dongen HP, Rogers NL, Banks S, Dinges DF. Time of day effects on neurobehavioral performance during chronic sleep restriction. *Aviat Space Environ Med.* Aug 2010;81(8):735-744.
23. Asch DA, Parker RM. The Libby Zion case. One step forward or two steps backward? *N Engl J Med.* Mar 24 1988;318(12):771-775.
24. Eden J, Berwick D, Wilensky G. *Graduate Medical Education That Meets the Nation's Health Needs*: National Academies Press; 2014.
25. Basner M, Babisch W, Davis A, et al. Auditory and non-auditory effects of noise on health. *Lancet.* Apr 12 2014;383(9925):1325-1332.

26. Volpp KG, Shea JA, Small DS, et al. Effect of a protected sleep period on hours slept during extended overnight in-hospital duty hours among medical interns: a randomized trial. *JAMA.* Dec 5 2012;308(21):2208-2217.

27. Rogers AE, Hwang WT, Scott LD, Aiken LH, Dinges DF. The working hours of hospital staff nurses and patient safety. *Health Aff (Millwood).* Jul-Aug 2004;23(4):202-212.

28. Landrigan CP, Rothschild JM, Cronin JW, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med.* Oct 28 2004;351(18):1838-1848.

29. Shea JA, Willett LL, Borman KR, et al. Anticipated consequences of the 2011 duty hours standards: views of internal medicine and surgery program directors. *Acad Med.* Jul 2012;87(7):895-903.

30. Volpp KG, Rosen AK, Rosenbaum PR, et al. Mortality among patients in VA hospitals in the first 2 years following ACGME resident duty hour reform. *JAMA.* Sep 5 2007;298(9):984-992.

31. Volpp KG, Rosen AK, Rosenbaum PR, et al. Mortality among hospitalized Medicare beneficiaries in the first 2 years following ACGME resident duty hour reform. *JAMA.* Sep 5 2007;298(9):975-983.

32. Friedman RC, Bigger JT, Kornfeld DS. The intern and sleep loss. *N Engl J Med.* Jul 22 1971;285(4):201-203.

33. Philibert I, Friedmann P, Williams WT. New requirements for resident duty hours. *JAMA.* Sep 4 2002;288(9):1112-1114.

34. Prasad M, Iwashyna TJ, Christie JD, et al. Effect of work-hours regulations on intensive care unit mortality in United States teaching hospitals. *Crit Care Med.* Sep 2009;37(9):2564-2569.

35. Press MJ, Silber JH, Rosen AK, et al. The impact of resident duty hour reform on hospital readmission rates among Medicare beneficiaries. *J Gen Intern Med.* Apr 2011;26(4):405-411.

36. Rosen AK, Loveland SA, Romano PS, et al. Effects of resident duty hour reform on surgical and procedural patient safety indicators among hospitalized Veterans Health Administration and Medicare patients. *Med Care.* Jul 2009;47(7):723-731.

37. Silber JH, Rosenbaum PR, Rosen AK, et al. Prolonged hospital stay and the resident duty hour rules of 2003. *Med Care.* Dec 2009;47(12):1191-1200.

38. Volpp KG, Rosen AK, Rosenbaum PR, et al. Did duty hour reform lead to better outcomes among the highest risk patients? *J Gen Intern Med.* Oct 2009;24(10):1149-1155.

39. Silber JH, Romano PS, Itani KM, et al. Assessing the effects of the 2003 resident duty hours reform on internal medicine board scores. *Acad Med.* Apr 2014;89(4):644-651.

40. Nasca TJ, Day SH, Amis ES, Jr. The new recommendations on duty hours from the ACGME Task Force. *N Engl J Med.* Jul 8 2010;363(2):e3.

41. Bellini LM, Baime M, Shea JA. Variation of mood and empathy during internship. *JAMA.* Jun 19 2002;287(23):3143-3146.

42. Bellini LM, Shea JA. Mood change and empathy decline persist during three years of internal medicine training. *Acad Med.* Feb 2005;80(2):164-167.

43. Bellini LM, Shea JA. Improvement of resident perceptions of nurse practitioners after the introduction of a collaborative care model: a benefit of work hour reform? *Teach Learn Med.* Summer 2006;18(3):233-236.

44. Borman KR, Biester TW, Jones AT, Shea JA. Sleep, supervision, education, and service: views of junior and senior residents. *J Surg Educ.* Nov-Dec 2011;68(6):495-501.

45. Borman KR, Jones AT, Shea JA. Duty hours, quality of care, and patient safety: general surgery resident perceptions. *J Am Coll Surg.* Jul 2012;215(1):70-77; discussion 77-79.

46. Castiglioni A, Bellini LM, Shea JA. Program directors' views of the importance and prevalence of mentoring in internal medicine residencies. *J Gen Intern Med.* Jul 2004;19(7):779-782.

47. Rosen IM, Gimotty PA, Shea JA, Bellini LM. Evolution of sleep quantity, sleep deprivation, mood disturbances, empathy, and burnout among interns. *Acad Med.* Jan 2006;81(1):82-85.

48. Shea JA, Frenkel EP, Webster GD. Training and practice activities of hematology and medical oncology diplomates. *Arch Intern Med.* Jan 1990;150(1):145-148.

49. Shea JA, Stern DT, Klotman PE, et al. Career development of physician scientists: A survey of leaders in academic medicine. *The American Journal of Medicine.* 2011;124(8):779-787.

50. Irani JL, Mello MM, Ashley SW, Whang EE, Zinner MJ, Breen E. Surgical residents' perceptions of the effects of the ACGME duty hour requirements 1 year after implementation. *Surgery.* Aug 2005;138(2):246-253.

51. Stamp T, Termuhlen P, Miller S, et al. Before and after resident work hour limitations: an objective assessment of the well-being of surgical residents. *Curr Surg.* Jan-Feb 2005;62(1):117-121.

52. Ripp J, Babyatsky M, Fallar R, et al. The incidence and predictors of job burnout in first-year internal medicine residents: a five-institution study. *Acad Med.* Oct 2011;86(10):1304-1310.
53. Block L, Wu AW, Feldman L, Yeh HC, Desai SV. Residency schedule, burnout and patient care among first-year residents. *Postgrad Med J.* Sep 2013;89(1055):495-500.
54. Lin GA, Beck DC, Stewart AL, Garbutt JM. Resident perceptions of the impact of work hour limitations. *J Gen Intern Med.* Jul 2007;22(7):969-975.
55. Ratanawongsa N, Bolen S, Howell EE, Kern DE, Sisson SD, Larriviere D. Residents' perceptions of professionalism in training and practice: barriers, promoters, and duty hour requirements. *J Gen Intern Med.* Jul 2006;21(7):758-763.
56. Maslach C, Jackson SE, Leiter MP. Maslach burnout inventory manual. 1996.
57. Gillberg M, Kecklund G, Akerstedt T. Relations between performance and subjective ratings of sleepiness during a night awake. *Sleep.* Apr 1994;17(3):236-241.
58. Basner M, Dinges DF, Mollicone D, et al. Mars 520-d mission simulation reveals protracted crew hypokinesis and alterations of sleep duration and timing. *Proc Natl Acad Sci U S A.* Feb 12 2013;110(7):2635-2640.

Consortium/Contractual Arrangements

The University of Pennsylvania will subcontract with Johns Hopkins University (Sanjay Desai, PI), The Brigham and Women's Hospital (David Bates, PI), and Pulsar Informatics, Inc (Daniel Mollicone, PI) for the iCOMPARE clinical trial.

Johns Hopkins University:

Dr. Desai is the Director of the Osler Medical Training Program at the Johns Hopkins Hospital, Vice Chair of Education for the Department of Medicine, and Assistant Professor of Medicine in the Johns Hopkins School of Medicine. He oversees 140 medicine trainees and over 200 subspecialty fellows. He led the residency program at Hopkins through the most recent changes in duty hour policy. He has won numerous teaching awards and has published widely on graduate medical education topics, with a specific focus on duty hour regulations, including a seminal 2013 single site crossover design study suggesting that stricter duty hour rules increased sleep duration among residents, but decreased patient continuity, educational opportunities, and perceived quality of care. Dr. Desai will chair the Executive Committee and collaborate with Drs. Asch and Shea in the leadership activities for the proposed project. He will work closely with Dr. Shea to specify the details related to the education outcomes and he will be the primary liaison to relevant organizations such as APDIM, ACGME and ACP. Dr. Desai will have a full-time research assistant at Johns Hopkins University.

Dr. Pronovost is the Director of the Armstrong Institute for Patient Safety and Quality at Johns Hopkins and Johns Hopkins Medicine's senior vice president for patient safety and quality. Dr. Pronovost is well known for his simple but effective checklist protocol that virtually eliminated central line catheter infections. He will advise on the science and design of the iCOMPARE trial and sit on the Steering Committee.

The Brigham and Women's Hospital:

Dr. Bates is Chief of the Division of General Internal Medicine and Primary Care and Chief Quality Officer at Brigham and Women's Hospital and Professor of Medicine at Harvard Medical School. He is an internationally known expert in medication safety, patient safety, evaluation, and clinical informatics, and he has also done extensive work on improving efficiency, quality, and on assessing health information technology (HIT) adoption and issues around interoperability. He did some of the leading work demonstrating the effects of implementation of computerized physician order entry on medication safety. He has also published on the effects of sleep on errors and adverse events. He is an elected member of the Institute of Medicine and serves as external lead for patient safety research for the World Health Organization. He will serve on the Steering Committee and provide key input regarding the time-in-motion portion of the study as well as all safety related issues.

Dr. Katz is the Director of the Internal Medicine Residency and Vice Chair for Education at Brigham and Women's Hospital. He is Associate Professor of Medicine at Harvard Medical School, where he holds the Marshall A. Wolf Chair in Medical Education. He has received numerous teaching awards, including the "Best Clinical Instructor at Harvard Medical School," which is voted on by the graduating class, five times. As an original member of the Harvard Work Hours, Health and Safety Group, he has contributed to research on the impact of duty-hour reform on health care provider physiology and patient safety. Other areas of research focus include physician professionalism, physician burnout, curriculum innovation and novel training experiences. He served on the leadership boards of the Association of Program Directors in Internal Medicine and the Massachusetts Medical Society Committee on Medical

Education. Dr. Katz has worked with the team since the inception to design the proposed iCOMPARE trial. He will sit on the Steering Committee and participate in the development of education outcomes, as well as assist in detailing the implementation plan across the 58 programs

Pulsar Informatics, Inc.

Pulsar Informatics, Inc., a company with extensive experience in fatigue management studies, will provide essential support for this trial, under the direction of Daniel Mollicone, PhD. Dr. Dinges has worked with Dr. Mollicone and Pulsar on multiple studies for over a decade and the company was subcontracted and played a key role in the recent mandatory sleep trial led by Drs. Volpp and Shea. Initially, Pulsar will develop a fatigue management didactic and site user manuals, train site personnel in the protocol, and configure and deploy equipment. In later years, Pulsar will be responsible for software maintenance, quality control, project management, and data upload for the sleep primary data collection from the participating sites to its secure servers.

All proposed consortium participants understand and agree to the following statement: The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

Resource Sharing Plans

1) *Data Sharing Plan*

Implementation of the NIH guideline regarding resource sharing requires discussions with study investigators and NIH program staff to determine which resources are appropriate for sharing and to arrive at acceptable methods for sharing specific types of resources. Resource sharing includes sharing of data, specimens, images, and other participant information but also includes sharing of study documents (recruitment materials, protocols, standard operating procedure documents, consents, forms, etc.) which may be useful as starting points for other studies. Resource sharing also includes dissemination of study results.

Data

Data to test the iCOMPARE hypotheses will come from interns, PGY2 and PGY3 residents, faculty, program directors, and patients and will include data collected directly by iCOMPARE as well as data collected by other sources originally for other purposes and now leveraged by iCOMPARE for a new purpose (e.g., Medicare data will be used to assess patient mortality; ITE test scores for trainees after their intern year will be obtained from the ACP and used to assess education outcomes; end of year questionnaires for trainees and faculty will be obtained from the ACGME to assess training quality). Some of these data will be at the individual level and some will be group-level data.

Because we are leveraging data collected by others for iCOMPARE's purposes, we will need to explore with each provider the terms of use for their data – how those data may be shared within the iCOMPARE group and how those data could possibly be shared in a public repository. The iCOMPARE group will work with the data providers to maximize the data available for internal sharing within the iCOMPARE Steering Committee and for public deposit. Where iCOMPARE collects the data directly, we will request consent for deposit of de-identified data in a public repository; for example, trainee consent to participate in actigraphy or time-motion studies will include consent to share de-identified data. Electronic surveys could include an informational statement about how the data about to be requested will be used and the respondent may opt out of the survey if unwilling to accept the terms of use. Where data collected by another group are provided to iCOMPARE, the group providing the data will be approached about sharing data; if all of the data provided to iCOMPARE may not be shared,summary data, a subset of data, or some analytic data removed from individual level may be shareable and useful to other researchers. We will work to maximize the data available for sharing.

All iCOMPARE investigators will be given access to cleaned datasets of data approved for sharing within the iCOMPARE group by the end of the trial funding. For example, data sets for internal data sharing with iCOMPARE investigators may be housed on the iCOMPARE website behind a password.

For sharing with scientists outside of the iCOMPARE group, to the extent permitted, we will prepare de-identified datasets by the end of the funding period for deposit at the NHLBI BioLINCC repository (https://biolincc.nhlbi.nih.gov/home/).

The DCC group has previously prepared datasets and associated documentation for deposit at BioLINCC for other NHLBI funded trials (NETT [National Emphysema Treatment Trial], CAMP [Childhood Asthma Management Program], and studies from the ACRC [Asthma Clinical Research Centers]) in accordance with NHLBI requirements for de-identification. The DCC has also provided NIDDK with public use datasets for NIDDK sponsored trials (NASH CRN). De-identification strategies we use in preparing the datasets include (but were not limited to) exclusion of participant name, SSN, Medicare number, clinic name, and similar identifiers; creation of new participant identification numbers; conversion of all dates to a number of days before or after randomization (or another appropriate reference date); deletion of comment fields; and collapse of categories with a number of subjects less than a certain threshold. The datasets are in SAS Transport format and are accompanied by documentation such as a data dictionary, blank case report forms, and explanatory notes. DCC staff have assisted users of the data sets as needed for particular issues and as requested by BioLINCC staff.

Study documents

Study documents created by iCOMPARE could be valuable to other sleep researchers and researchers in related fields. The CCC and DCC will facilitate appropriate access to study materials (data, documents, results etc.) once released by the iCOMPARE Steering Committee and NHLBI. Once released for sharing, materials (as allowed by copyright protections) will be posted to the public area of the study website for downloading in PDF or other format or deposited with National Technical Information Service (NTIS). Materials at NTIS are available forever; study specific websites will go dark once resources to support the study are exhausted.

Dissemination of study results

This project has direct clinical and policy relevance. If the hypotheses of the proposal are supported, we expect that the ACGME will revisit the current duty hour standards and, informed by the results of this trial, consider extending the flexibility of intern duty hours in the direction of the intervention arm. Rarely do individual studies have such an immediate connection to broad and important health care change. Such a change in policy will affect every teaching hospital in the United States, and every patient.

We will aim for dissemination of results through the traditional academic channels of journal publication and presentation at scientific meetings as well as through news media. We will also partner with the Leonard Davis Institute of Health Economics—an institute at the University of Pennsylvania that connects its School of Medicine (Perelman) to its business school (Wharton) and Schools of Nursing, Law, and Communication (Annenberg)—to extend the reach of our findings to members of Congress and leaders in health care who are unlikely to receive or read academic journals but who would value the results of this trial and are in positions to create change in other relevant areas.

In addition to public dissemination through media outlets, we will ensure that the results are available to the public by posting summary results on clinicaltrials.gov.

2) Sharing Model Organisms

Not applicable

3) Genome Wide Association Studies (GWAS)

Not applicable