Study of Osteoporotic Fractures (SOF)
Publications Guidelines

I. GOALS

1. To encourage high quality publications and presentations.
2. To encourage broad participation by investigators in publications and presentations.
3. To encourage creative use of the data.

II. SCOPE OF THE GUIDELINES

The policy covers papers, abstracts, oral and poster presentations that involve unpublished data collected as part of the SOF study and details three different pathways for accessing SOF data. These policies will remain in force even after funding for SOF ends.

III. THREE PATHWAYS FOR ACCESSING SOF DATA

1. Use the limited public release dataset available on SOF Online: https://sofonline.ucsf.edu
2. To access the full SOF dataset and to benefit from the review of experienced SOF investigators, submit an analysis plan (and all related publications) to the Coordinating Center for Publications Committee approval.
3. For students and investigators affiliated with a SOF clinical site, work closely with local SOF investigators and receive local approval for analysis plans and publications, along with access to local copies of the SOF dataset.

IV. PATHWAY 1: SOF ONLINE

A. To access data on SOF Online (https://sofonline.ucsf.edu), you must create an account and electronically sign a Data Use Agreement.
B. Public data release (PDR) datasets are accessible in the "Data & Documentation" section of the website. This section also includes links to:
    i. Data collection forms
    ii. "Longitudinal Data Documentation" to browse variables in the data set
C. The PDR datasets have the following limitations:
    i. Extreme values (such as age, height, weight) that could possibly identify a participant have been removed from the datasets.
    ii. The datasets do not include all data generated from ancillary studies and substudies.
    iii. Data collected from bi-annual phone follow-up questionnaires (2009-2016) are not available.
    iv. Adjudicated MCI and dementia data generated from the SOF Sleep and Cognition in Older Women substudy are not available.

V. PATHWAY 2: SOF PUBLICATIONS COMMITTEE REVIEW

To benefit from the review of experienced SOF investigators and to access the full dataset, investigators may submit an analysis plan and any related publications to the Publications Committee for approval. The following sections describe the process and requirements.

A. PUBLICATIONS COMMITTEE

A majority of members on the Publications Committee will be investigators from Clinical Centers. Changes in leadership and membership will be subject to approval by the Steering Committee**.** Please see Appendix A for a list of current members.

B. AUTHORSHIP

1. Definition of authorship. Authors must participate in the writing of the paper in accordance with the International Committee of Medical Journal Editors guidelines (N Engl J Med 1991;324:424-8). First authors are expected to delete names from the final list of authors if those individuals have not participated in the writing and/or analysis of the paper in accordance with those guidelines.

2. First authorship. First authorship will be decided on by the writing group of the project. In general, the investigator who first conceived of the project and submitted a plan for the manuscript to the Publications Committee should have the option of serving as first author. Conflicts in first authorship should be resolved by all members of the writing group.

3. Co-authorship. The first author may invite any investigator whom he/she feels has contributed significantly to the paper to join the list of authors at any time. It is encouraged to include investigators from the Coordinating Center or the clinical sites as an author on papers using study-wide data. The order of authorship on a paper should be determined by the writing group for that project.

4. Sponsorship
   a) A SOF Sponsor is required for all analysis plans submitted by non-SOF investigators. A list of eligible SOF Sponsors is included as Appendix B. The investigator submitting an analysis plan may propose a SOF Sponsor for their project or one will be assigned by the Coordinating Center once the plan is approved. Every effort to assign a sponsor that is most familiar with the study topic will be made. If the investigator suggests a SOF sponsor upon submitting the plan and the proposed sponsor is not available to work on the plan, an alternative sponsor may be assigned.
   b) The SOF Sponsor will serve as the main point person for communicating with the authors and is responsible for overseeing the progress of the plan and to ensure that scientific integrity is maintained. The sponsor also has the opportunity to serve as co-author.
   c) All eligible SOF Sponsors will be notified when plans are submitted and will be given the opportunity to request to serve as the Sponsor of the plan if one has not already been requested.

C. DATA USE AGREEMENT (DUA)

A DUA is required for all investigators who will be in contact with SOF data or will be analyzing SOF data for research purposes. The DUA should be signed by the institution releasing the data (California Pacific Medical Center (CPMC)) and the institution receiving the data. The DUA will

cover all investigators and/or staff working with SOF data under the direct supervision of the lead investigator of a DUA at a given institution.

There are a few exceptions. Investigators who have a subcontract or consulting agreement under CPMC for work with the SOF Study may not be required to complete a DUA. In addition, investigators conducting a meta-analysis, who will never receive participant level data from the SOF Study, may not be required to sign a DUA.

The Coordinating Center will ensure that DUAs are in place with all investigators and analysts working with SOF data. It is the responsibility of the lead investigator at a given institution to obtain the appropriate signatures at their local institution and to ensure that his/her staff comply with the terms of the agreement.

D. Availability and Analysis of Data

Unless otherwise noted by the Coordinating Center, proposals for analysis plans can only be submitted based on data that has officially been released for analysis by the Coordinating Center.

SOF sites will also have copies of released datasets. The site PI will have the authority to grant other site investigators access to their copy of the datasets.

E. Assignment and Approval Process

All analysis of SOF data for abstracts, posters, slides or manuscripts may not commence until an analysis plan has been approved. Approval of analysis plans may occur centrally by the Publications Committee or locally at the SOF Clinical Centers.

Publications Committee Review:

1. The analysis plan should specify the research question, brief description of statistical methods and variables to be used in the analysis, and proposed tables. The submitter should indicate whether they will conduct the analyses locally, or would like to submit a request and provide funds for a Coordinating Center analyst to analyze the data. In some situations, the submitter may be asked by the Coordinating Center to provide more detailed information about the plan, such as proposed tables.

   The plan will be initially reviewed by the Coordinating Center (to alert the submitter to potential conflicts or overlapping projects, if any, or problems of feasibility).

2. After initial review, the plan will be distributed to all Publications Committee members for approval. All members of the Publications Committee can review plans and vote on approval. However, one primary reviewer will be assigned to carefully review the plan and provide comments to the author. The primary reviewer will have two weeks to review a submitted analysis plan.

   If any member of the Publications Committee does not accept the proposed plan, the first author must consider revisions and resubmit the plan. If necessary, final approval of an analysis plan will require a majority vote of the Steering Committee.

3. Should it become necessary to revise an analysis plan, the author should submit a proposal for modification to the Publications Coordinator that highlights the changes in the text of the original analysis plan. The revised proposal will then be reviewed as described above.

F. Review of Abstracts, Posters, Slides and Manuscripts

Manuscripts and abstracts, posters, and slides to be presented at national and international meetings must be approved by the Publications Committee (for centrally approved analysis plans) or by the local site PI (for locally approved analysis plans) prior to submission or presentation. (Slides and other materials which are prepared for small, informal meetings or invited presentations need not be approved by the SOF Publications Committee.)

Publications Committee Review:

1. The primary investigator should send the completed abstract, poster, slides or manuscript to all co-authors for review. After incorporating the changes from the co-authors, the primary investigator should send the final version of the abstract, poster, slides or manuscript to the Coordinating Center. Materials must be submitted at least 4 weeks prior to the submission deadline or presentation date.

2. The Coordinating Center will send the final draft of the abstract, poster, presentation or manuscript to the assigned primary reviewer for approval. The primary reviewer should communicate their approval or disapproval by email within two weeks from the date that is sent.

   If the reviewer recommends that changes be made, it is the investigator's responsibility to implement the revisions and submit a revised version to the reviewer through the Coordinating Center.

3. It is the responsibility of the primary investigator to keep the Coordinating Center informed of any acceptances, rejections or resubmission of the abstract, poster, slides or manuscript. If a manuscript is substantially changed for resubmission, it should be submitted to the Coordinating Center to be re-approved by the assigned reviewer.

G. Use of SOF Data for Pooled Analyses with Data from Other Studies

Occasionally investigators may be interested in using SOF data for pooled analyses with data from other studies. These research proposals, even if they overlap with previous analysis plans, should be submitted under a separate analysis plan for approval, and are subject to the same guidelines for approval, use of SOF data, and review as all other SOF analysis plans.

In cases where the lead author on the analysis is not a SOF investigator, the participating SOF author should serve as the sponsor of the analysis. All abstracts, posters, slides and manuscripts are subject to the same review process as all SOF analyses, and it is the responsibility of the SOF sponsor on the analysis plan to notify the other researchers of this condition, and to facilitate the review and approval process according to the guidelines.

VI. Pathway 3: Local Site Review

SOF sites have oversight over analyses to be completed locally. The site PI or designee has the authority to review and approve analysis plans proposed by investigators and students at their site. While these analysis plans do not need to be submitted to the Publications Committee for review, the sites will be responsible for sending locally approved plans to the Coordinating Center to be included in a centralized archive of analysis plans.

All abstracts, posters, slides, or manuscripts generated from locally approved analysis plans must be reviewed and approved by co-authors as well as the SOF PI or designee. The SOF PI or designee will inform the Coordinating Center of any manuscripts accepted for publication.

VII. OFFICIAL STUDY NAME, REQUIRED ACKNOWLEDGEMENTS, AND RECOMMENDED TERMINOLOGY

A. The official name of the study for scientific purposes is the “the Study of Osteoporotic Fractures (SOF).” All papers should include "the Study of Osteoporotic Fractures" in the title or "for the Study of Osteoporotic Fractures" in the authorship line. For meta-analyses, the study should be included in an acknowledgement.

B. All study-wide papers, abstracts, and presentations (oral and poster) should include the acknowledgement: ‘The Study of Osteoporotic Fractures (SOF) is supported by National Institutes of Health funding. The National Institute on Aging (NIA) provides support under the following grant numbers: R01 AG005407, R01 AR35582, R01 AR35583, R01 AR35584, R01 AG005394, R01 AG027574, and R01 AG027576.’

C. All papers, abstracts and presentations (oral and poster) that include data from the SOF Sleep Study should include in the acknowledgement: ‘The Study of Osteoporotic Fractures (SOF) is supported by National Institutes of Health funding. The National Institute on Aging (NIA) provides support under the following grant numbers: R01 AG005407, R01 AR35582, R01 AR35583, R01 AR35584, R01 AG005394, R01 AG027574, R01 AG027576, and R01 AG026720.’

VIII. NIH PUBLIC ACCESS POLICY

The NIH Public Access Policy states that all NIH-funded studies must submit copies of their manuscripts to the digital archive PubMed Central (PMC) once accepted for publication to a peer-reviewed journal. Authors should review the journal's copyright agreement before signing and determine if they allow for submission to PMC. If not, it is the author’s responsibility to negotiate with the journal to make sure this is allowable.

Once accepted for publication, the manuscript should be submitted to the NIH Manuscript Submission system at http://www.nihms.nih.gov. The manuscript will be assigned a PMCID. The Coordinating Center should be notified of the PMCID as soon as it is available. For more information on the NIH Public Access Policy, please visit http://publicaccess.nih.gov.

IX. REVISIONS

The Steering Committee will approve revisions of these guidelines by majority vote.

Appendix A
SOF Publications Committee Members
April 2018

Steve Cummings (Chair, San Francisco Coordinating Center)

Sonia Ancoli-Israel (University of California, San Diego)
Doug Bauer (San Francisco Coordinating Center)
Dennis Black (San Francisco Coordinating Center)
Jane Cauley (Pittsburgh Clinical Center)
Peggy Cawthon (San Francisco Coordinating Center)
Susan Diem (Minneapolis Clinical Center)
Kris Ensrud (Minneapolis Clinical Center)
Dan Evans (San Francisco Coordinating Center)
Howard Fink (Minneapolis Clinical Center)
Lisa Fredman (Boston University)
Teresa Hillier (Portland Clinical Center)
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Erin LeBlanc (Portland Clinical Center)
Lily Lui (San Francisco Coordinating Center)
Michael Nevitt (San Francisco Coordinating Center)
Kathy Pedula (Portland Clinical Center)
Susan Redline (Brigham and Women's Hospital)
John Schousboe (Minneapolis Clinical Center)
Katie Stone (San Francisco Coordinating Center)
Brent Taylor (Minneapolis Clinical Center)
Greg Tranah (San Francisco Coordinating Center)
Kim Vesco (Portland Clinical Center)
Kristine Yaffe (University of California, San Francisco)

Appendix B
Eligible SOF Sponsors
September 2009

Steve Cummings (Chair, San Francisco Coordinating Center)

Doug Bauer (San Francisco Coordinating Center)
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Jane Cauley (Pittsburgh Clinical Center)
Peggy Cawthon (San Francisco Coordinating Center)
Kris Ensrud (Minneapolis Clinical Center)
Lisa Fredman (Boston University)
Teresa Hillier (Portland Clinical Center)
Marc Hochberg (Baltimore Clinical Center)
Nancy Lane (San Francisco Coordinating Center)
Michael Nevitt (San Francisco Coordinating Center)
Katie Stone (San Francisco Coordinating Center)
Kristine Yaffe (University of California, San Francisco)
Joe Zmuda (Pittsburgh Clinical Center)

Appendix C
SOF Analysis Plan Examples

Example # 1

Research Aims:

1. Are baseline levels of total and bioavailable estradiol, estrone, and total and bioavailable testosterone associated with incident diabetes?
2. Does body weight mediate the relationship between sex hormones and diabetes?

Hypotheses: Women with the lowest quartile values of estradiol and highest quartile values of testosterone will have the highest risk of incident diabetes. This effect, in part, will be mediated by total body fat and abdominal fat.

Background:

Menopause is associated with a decrease in the absolute concentrations of most endogenous sex hormones in women. Menopausal estrogen deficiency has been associated with an acceleration of visceral fat accumulation [Tchernof, 1998]. A surrogate measure of visceral adiposity, waist circumference, has demonstrated the best correlation to visceral fat content [Pouliot, 1994][Anderson, 1997] and is related to dyslipidemia and changes in glucose and insulin homeostasis. There is strong epidemiologic and pathophysiologic evidence linking visceral adiposity with insulin resistance and diabetes.[Kissebah, 1996][Rios, 1998][Montague, 2000]

Increased androgenicity in women as measured by increased bioavailable testosterone or decreased sex hormone-binding globulin levels is associated with visceral adiposity.[Jensen, 2000] Increased androgenicity is also associated hyperglycemia, hyperinsulinemia, insulin resistance and dyslipidemia in diabetic women and in non-diabetic women with polycystic ovaries.[Evans,1983][Change,1983] However, the mechanism of association between androgenicity and visceral obesity still remains unclear.

Hormone replacement therapy (HRT) has been shown to prevent central distribution of body fat in randomized controlled trials though total body fat stores remain largely unchanged.[Haarbo, 1991][PEPI, 1995][HERS, unpublished data] Recently, we found that randomization to HRT decreased the 4-year incidence of diabetes in postmenopausal by maintaining fasting glucose levels over time.[HERS, unpublished data] However, the beneficial changes observed in abdominal obesity with HRT did not mediate this lower incidence of diabetes.

We hypothesize that postmenopausal women enrolled in SOF with higher endogenous estradiol levels will have lower 10-year incidence of diabetes than those with lower levels. Additionally, women with increased bioavailable testosterone will have the highest incidence of diabetes. Higher levels of visceral fat, measured by waist circumference, may mediate this effect.

Predictor Variables: Total and bioavailable estradiol, total estrone, total and bioavailable testosterone and Sex Hormone Binding Globulin (SHBG) at baseline.

Outcome Variables: Self-report diabetes at year 10 or use of a diabetes medication

Covariates: body fat measured by Bioelectric Impedance Analysis (year 2 or year 5), BMI (year 1 and 10), waist circumference (year 1) , hip circumference (year 1), cigarette smoking, alcohol use, physical activity, medication inventory (use of thiazide diuretics, beta-blockers, ACEI, statins, HRT, corticosteroids)

Analytic Plan:

Aim #1:

Methods: Women with known diabetes at baseline or those using hormone replacement therapy at baseline or at any time during the 10-year follow-up period will be excluded from these analyses.

Baseline sex hormone assays have been previously evaluated in SOF in two case-cohort studies. The first study [Cummings, *NEJM*, 1998] randomly sampled approximately 270 cases of women who had a first hip fracture or new vertebral fracture during 5.9 years of follow-up and compared their sex hormone levels with 359 randomly sampled controls. The second study [Cauley, *Ann Int Med*, 1999] evaluated the effect of endogenous hormone levels on incident breast cancer. Their sampling scheme included all 97 consecutive cases of incident breast cancer at 3.2 years of follow-up and 247 randomly sampled controls. The hormonal assays were performed on the baseline stored sera at different labs (Endocrine Sciences and Corning Nichols Institute, respectively) approximately 7-8 years after collection.

Since the sampling scheme of the first case-cohort study may pose inherent bias to our study question, in that hip fracture has been associated with diabetes in this cohort [Schwartz, 2001], we will stratify our analysis of these hormonal assays by case/control status. If the results are similar in direction of association, we will combine the two groups to increase power. Since breast cancer is not associated with incident diabetes, we will combine both study groups from this case-cohort study and analyze this population separately from the first. If findings are similar from both of these study populations, we will combine the groups and adjust for laboratory site. Additionally, we will do separate analyses combining only the randomly selected controls of each case-cohort study, adjusting for laboratory site, to confirm our findings.

Using Cox proportional hazards models, separate models will be constructed for each hormone assay to evaluate its effect on incident diabetes. We will evaluate the predictors both as continuous and categorical (in quartiles) variables. We will adjust for known confounders in the association such as age, race, current smoking, alcohol use.

Aim #2:

In additional Cox models, we will add a baseline measure of body fat (BMI) and the change in this measurement at year 10 to evaluate potential mediation. In separate models we will evaluate other surrogate measures for total body fat (bioelectric impedance) and abdominal fat (waist circumference, or waist-hip ratio).

Mock Tables:

Table 1: Baseline characteristics of women with hormone assays (excludes known diabetics or those on HRT or corticosteroids)

	Fracture case-cohort	Breast ca. case-cohort	p-value*
Age (year) Weight (kg) BMI (kg/m2) Body fat by BIA Current smoker (%) Alcohol use (# dr/wk) Physical activity Median hormone levels: Total Estradiol (pg/ml) Free estradiol (pg/ml) Non-SHBG-bound E2 Estrone (pg/ml) Total testosterone (pg/ml) Bioavailable testosterone SHBG (ug/dl) Incident cases of Diabetes (n):			

Example # 2:

Background:

Bone mineral density is known to be strongly correlated with increased breast cancer risk based on SOF and other data. [1, 2]. Preliminary evidence also suggests that osteoporotic fractures and late life height loss are associated with endometrial cancer[3]. Thus bone mineral density, perhaps as a marker of cumulative hormone exposure, may predict increased risk of estrogen-related cancers.

Preliminary evidence also suggests that bone mineral density may also be associated with colon cancer risk, however the association appears to be in the opposite direction [4]. In a small study of the Framingham cohort, Zhang et al found that women with the highest bone mass as measured by wrist radiography had the lowest risk of colon cancer. These investigators proposed that bone mass is a marker of estrogen exposure and cite observational data which suggests that hormone replacement therapy is associated with decreased risk of colon cancer.

A previous analysis of SOF data suggests that osteoporotic spine fractures are associated with an increased risk of overall mortality, and, in particular, cancer mortality [5]. This suggests that lower bone mineral density may also be associated with increased risk of cancer death. However, it is possible that while lower bone mineral density is associated with a higher overall risk of cancer deaths, it is associated with increased risk of death from some subtypes of cancer. In particular, based on the preliminary evidence of other studies, it appears that lower bone mineral density may be associated with decreased risk of hormonally driven cancers such as breast and endometrial cancers and associated with increased risk of colon and other cancer deaths.

Hypothesis:

Increased bone mineral density, as a marker of cumulative hormonal exposure is associated with increased risk of estrogen-related cancer deaths (breast, endometrial, and ovarian) and associated with decreased risk of other cancer deaths.

Analysis Plan:

Bone mineral density at the hip and spine will be entered into a Cox regression model as the primary predictors. Several outcomes will be considered including all cancer deaths, deaths from estrogen-related cancers and deaths from non-estrogen related cancers. We will plan on grouping them together as either estrogen-related cancers (breast, ovarian and endometrial) and non-estrogen related cancers (lung, colon, other). In addition, depending on the absolute numbers of individual cancers we will also consider colon cancer and lung cancer deaths individually. Potential confounders we will consider include age, smoking status, alcohol use, body mass index, parity history, age at menopause, age at menarche, education level.
We will use cancer deaths with the knowledge that any association may imply that bone mineral density can be associated with either increased cancer risk or increased risk of progression from cancer. Thus, any positive results with this analysis will require more detailed study to determine whether the association is due to cancer risk or risk of progression.

Who will do the analysis: Coordinating Center

REFERENCES:

1. Cauley, J.A., *et al.*, *Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group.* Jama, 1996. **276**(17): p. 1404-8.
2. Zhang, Y., *et al.*, *Bone mass and the risk of breast cancer among postmenopausal women.* N Engl J Med, 1997. **336**(9): p. 611-7.
3. Newcomb, P.A., *et al.*, *Fracture history and risk of breast and endometrial cancer.* Am J Epidemiol, 2001. **153**(11): p. 1071-8.
4. Zhang, Y., *et al.*, *Bone mass and the risk of colon cancer among postmenopausal women: the Framingham study.* Am J Epidemiol, 2001. **153**(1): p. 31-7.
5. Kado, D.M., *et al.*, *Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group.* Arch Intern Med, 1999. **159**(11): p. 1215-20.