Report

2010 Annual Membership Meeting
15 April 2010
Washington, DC

Consumers United for Evidence-based Healthcare (CUE)
U. S. Cochrane Center

This meeting was sponsored by the Agency for Healthcare Research and Quality (AHRQ)
(Grant # 1R13 HS017668-01A)
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(i) Abbreviations used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<td>CER</td>
<td>Comparative effectiveness research</td>
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<td>CFAH</td>
<td>Center for Advancing Health</td>
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<td>CUE</td>
<td>Consumers United for Evidence-based Healthcare</td>
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<tr>
<td>EBHC</td>
<td>Evidence-based healthcare</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>USCC</td>
<td>US Cochrane Center</td>
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(ii) Appendices

Appendix A: CUE Annual Membership Meeting agenda
Appendix B: CUE Annual Membership Meeting speakers
Appendix C: CUE Accomplishments September 2009 - April 2010 - PowerPoint presentation
Appendix D: Engagement – Do people engage to get the care they need? - PowerPoint presentation
Appendix E: When can we consider RCT data sufficient to assess effectiveness and harm and when is more information needed? - PowerPoint presentation
Appendix F: Current practices of consumer involvement in systematic reviews - opportunities and challenges - PowerPoint presentation
Appendix G: Who is a consumer and who gets to decide? - PowerPoint presentation
Appendix H: Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency - PowerPoint presentation
Appendix I: CUE Annual Membership Meeting evaluation survey instrument
1. **Overview**

The 2010 Annual Membership Meeting for Consumers United for Evidence-Based Healthcare (CUE), hosted by the US Cochrane Center (USCC), was held on April 15, 2010, at the Johns Hopkins University Carey Business School in Washington, DC. The meeting objectives were (1) to provide education and training on research and methodology that promote the inclusion of consumer advocates in scientific research, (2) to address administrative matters pertaining to CUE, and (3) to strengthen the infrastructure of CUE.

The Annual Membership Meeting afforded CUE members an opportunity to gain new knowledge and skills in evidence-based healthcare (EBHC), share information on successful programs and strategies, and meet and interact with potential scientist, policymaker, and government partners. We invited outside speakers to address critical issues in comparative effectiveness research (CER) and EBHC, for example, a well-known social scientist with an interest in understanding and enhancing patient engagement in personal healthcare and in the healthcare system (Jessie Gruman), a researcher studying the current practice of consumer involvement in systematic reviews (Julia Kreis), and an epidemiologist (Kay Dickersin) addressing when randomized controlled trial (RCT) data is and is not sufficient to assess effectiveness and harm (Rachel Fleurance). CUE members led workshops on *Who is a consumer, and who gets to decide?* (Barbara Warren and Tom Hill), and *Be a peer reviewer: Learn to do a critical appraisal of a Cochrane systematic review* (Maryann Napoli). An additional workshop on *Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency* was led by a health economist (Rachel Fleurance). CUE members also provided updates on their organizations’ activities in EBHC.

Throughout the meeting, examples of consumer participation in EBHC were presented and new opportunities were highlighted. Challenges were also noted, among them (1) CUE must identify consistent funding sources to provide the high quality education programs and resources; and (2) consumer advocacy organizations need to effectively engage in EBHC and CER, and to promote use of evidence among healthcare decision makers. CUE is poised to play a unique role as a credible source of information about evidence as an important tool for consumers, not as a means by which to take effective treatments away from consumers (see Appendix A, 2010 CUE Annual Membership Meeting Agenda, and Appendix B, 2010 CUE Annual Membership Meeting speakers).

2. **CUE Annual Membership Meeting agenda**

Kay Dickersin welcomed CUE members and guests and thanked them for their support and many contributions to CUE. Janie Gordon acknowledged the service of retiring CUE Co-
chairs Sallie Bernard (SafeMinds) and Barbara Warren (National Coalition for Lesbian, Gay, Bisexual, and Transgender Health). Both provided outstanding leadership during a period of growth in membership, reputation, and impact for CUE. New CUE Co-chairs Maureen Corry (Childbirth Connection) and John Santa (Consumers Union) were acknowledged.

2.1 Update on CUE activities - Maureen Corry, CUE Co-chair

Maureen Corry provided a snapshot of CUE’s accomplishments in education, advocacy, research and policy since the previous meeting, September 3, 2009 (see Appendix C, CUE Accomplishments September 2009 - April 2010 - PowerPoint presentation).

2.2 Keynote: Consumer engagement – Do patients engage with the healthcare system to get the care they need? - Jessie Gruman, President, Center for Advancing Health (CFAH)

Jessie Gruman noted that today’s healthcare system promises better outcomes but simultaneously demands more of patients. A patient must perform engagement behaviors, i.e. actions that an individual (not a health professional or institution) must take to obtain the benefits of available medical services. Dr. Gruman emphasized that “patient compliance” and “patient-centered care” are not equivalent to patient engagement.

CFAH developed a 10-point engagement behavior framework based on a literature search, interviews with 210 patients/caregivers, and with 37 key informants. The framework behaviors range from finding safe and decent care to making good treatment decisions to planning for end of life care. She pointed out that everybody needs to know what they are expected to do and many people need help to do them.

The CFAH team reviewed 21 national and four regional surveys in order to identify what behaviors patients were performing. Dr. Gruman reported that: (1) people are more likely to do simple tasks than complex tasks; (2) participation in all categories is shallow; (3) people prefer just in time actions; (4) predictable barriers (no insurance, ethnicity, poor health, low income) do not explain all non-participation; and (5) the meaning of Internet use is uncertain. In closing, Dr. Gruman implored the audience to teach and demonstrate the value of consumer participation in every venue where healthcare decisions are made (see Appendix D, “Engagement – Do people engage to get the care they need?” - PowerPoint presentation).
2.3 When can we consider RCT data sufficient to assess effectiveness and harm and when is more information needed? - Kay Dickersin, Director, US Cochrane

Kay Dickersin noted that her topic was requested by CUE members who had methodological questions stemming from the US Preventive Services Task Force’s (USPSTF) recent recommendations on breast cancer screening. To make the session most useful to participants, attendees were asked to submit study design questions prior to the meeting. Dr. Dickersin responded to as many of the questions as possible during her remarks. She referred participants interested in the use of data from different study designs (e.g., observational data) to attend Dr. Fleurence’s workshop in the afternoon.

Dr. Dickersin noted that to recognize “best evidence” we need to understand the type of question being asked and seek the appropriate evidence to answer each specific type of question. She said that to assess harm, evidence should be sought from clinical trials, followup studies and case control studies. She noted that clinical trials usually do not have large enough study populations or long enough followup to detect intervention harms.

Dr. Dickersin responded to a question about how trial results should be interpreted when the population studied is narrower than your population of interest? She explained that she asks when there are data on effectiveness available from a well-designed and conducted trial, “Is the population studied so different, is the intervention so different, is the setting so different that I would choose to ignore these findings in favor of believing there is no evidence on the topic?” In response to a question about how benefits and harms could be balanced when different groups assign different weights to harms (e.g., loss of fertility in younger and older women) she noted that evidence is not the only factor in EBHC; consideration is also given to clinical expertise and patient values. In response to a related question about subgroup analysis, she noted that subgroup analyses can be helpful in identifying future hypotheses to be studied.

A few questions addressed concerns that some studies minimize selection and information biases, but are problematic in other areas. For example, studies may employ a comparison intervention that puts the test intervention in a favorable light or statistically significant outcomes may be selectively reported. Dr. Dickersin commented that these are valid concerns, whether for industry or non-industry studies.

Asked how to interpret results from head-to-head trials (i.e., two active interventions compared) versus results from an active intervention compared to a placebo or no intervention, Dr. Dickersin commented that a head-to-head trial is appropriate when two interventions have already been shown to be effective when compared to placebo or no intervention in previous studies.
The final question discussed related to the relative merits of various adaptive designs. Dr. Dickersin clarified that adaptive designs are changes in a trial’s design or analysis guided by looking at the trial data while the study is ongoing. She noted that adaptive designs should always be preplanned with specific steps noted as to what exactly what will be done in various circumstances (see Appendix E, “When can we consider RCT data sufficient to assess effectiveness and harm and when is more information needed?” - PowerPoint presentation).

2.4 Introduction of CUE member organizations - John Santa, CUE Co-chair

John Santa asked each member to introduce him/herself and speak briefly about his/her organization’s current work in EBHC and CER. He noted the many outstanding initiatives underway.

2.5 Current practices of consumer involvement in systematic reviews - opportunities and challenges - Julia Kreis, Commonwealth Fund Harkness/Bosch Fellow

Julia Kreis shared findings from her research on consumer involvement in CER addressing these questions: What is the definition of a consumer? What is the rationale for involving consumers in health research? What are useful frameworks to describe consumer involvement in health research?, and How are consumers currently involved in systematic reviews?

From her literature review, Ms. Kreis found many definitions of “consumer” in the literature. The Cochrane Collaboration definition is “someone who uses, is affected by, or who is entitled to use a health-related service.” In the literature, there are two main rationales for including consumers: (1) to improve the quality of the research product, for example by taking into account the unique insights into an illness which patients can offer; and (2) to be politically and ethically “correct,” that is, those who pay for the research should have a voice in it and also that those who are ultimately affected by the research should have a say in it. Ms. Kreis also discovered two philosophically different perspectives on involving consumers (1) “consumerism” – a goal of increasing consumer satisfaction with the “product” and (2) empowerment – a goal of enabling consumers to exercise greater autonomy in decision making.

Ms. Kreis also conducted a survey about consumer involvement in systematic reviews, interviewing key informants from 15 US organizations, the Cochrane Collaboration, and Campbell Collaboration. The US-based organizations included AHRQ, the National Institutes of Health, several evidence-based practice centers, and private organizations carrying out systematic reviews, as well as professional societies and provider organizations. Interviewees were asked whether they involve consumers on a regular basis, and, if so, what processes they have in place and also what they see as the main rationale for involving consumers.
Results show that very few organizations involve consumers on a regular basis (5 in the sample surveyed). These were AHRQ, two evidence-based practice centers, the Cochrane Collaboration, and the Campbell Collaboration). Ms. Kreis noted that more evidence is needed on the impact of consumer participation in systematic reviews and raised questions for future study: What level of involvement is preferred from a consumer perspective? What if a consumer organization is not dedicated to principles of EBHC? Should consumers be involved as individuals or representatives of a constituency? (see Appendix F, “Current practices of consumer involvement in systematic reviews - opportunities and challenges” - PowerPoint presentation).

2.6 Workshops

Two sessions of three parallel workshops were offered, allowing each participant to make two workshop selections. Workshops addressed these topics: (1) Who is a consumer, and who gets to decide, (2) Be a peer reviewer: Learn to do a critical appraisal of a Cochrane systematic review, and (3) Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency.

2.6.1 Who is a consumer, and who gets to decide

Two experienced consumer advocates, Barbara Warren, National Coalition for Lesbian, Gay, Bisexual, and Transgender Health, and Tom Hill, Faces and Voices of Recovery, presented the workshop on defining “Who is a Consumer,” a topic of substantial interest to the evidence-based consumer advocacy movement. Dr. Warren and Mr. Hill explored the difference between a consumer advocate and a consumer patient/client and evoked considerable discussion. Participants shared their viewpoints about how to help consumers gain traction in highly professionalized environments and emphasized that consumers’ contributions must be noted and valued. The term “two-hatter” was introduced: a person who qualifies and may identify as a consumer, but is also a professional in a health-related field. The contexts in which it would and would not be acceptable or optimal for a “two-hatter” to assume a consumer role were discussed (see Appendix G, “Who is a consumer and who gets to decide?” - PowerPoint presentation).

2.6.2 Be a peer reviewer: Learn to do a critical appraisal of a Cochrane systematic review

Marianne Napoli, in her role as a consumer advocate, has participated as a peer reviewer for numerous reviews, across a variety of Cochrane review groups as well as other organizations. She shared her experiences as a Cochrane peer reviewer, explaining the steps of a review and the point at which she has been asked to contribute to the process. Ms. Napoli noted that she focuses her efforts primarily on the Plain Language Summary in Cochrane reviews, because it is what
most consumers read for information and guidance.

2.6.3 Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency

Rachael Fleurence conducts research that focuses on evidence synthesis methods, systematic reviews and meta-analyses including mixed treatment comparisons, cost-effectiveness analyses, and value of information methodology. She presented a workshop to follow up on some of the issues raised by Dr. Dickersin in the plenary session. Her objectives were to review the differences between randomized and observational evidence, and to provide practical steps to assess evidence to answer different types of research questions. Dr. Fleurance provided advice on how to navigate the literature to get the best answers to a question of interest. She used hormone therapy in post-menopausal women to prevent cardiovascular events as an example of where mistakes were made in assessing the available evidence. Dr. Flerance pointed out that had a rigorous system of rating the quality of evidence been applied, it would have shown that because the data came from observational studies with inconsistent results, the evidence for reduction in cardiovascular risk was of very low quality. She noted that randomized controlled trials showed that hormone therapy fails to reduce cardiovascular risk and may even increase it. She closed by emphasizing that critical thinking is essential to assessing evidence (see Appendix H, “Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency” - PowerPoint presentation).

2.7 Summary of CUE member evaluations

Twenty-three people attended the 2010 CUE Annual Membership. Participants were asked to complete a detailed evaluation form (see Appendix I, CUE Annual Membership Meeting evaluation survey instrument).

Ten participants returned the evaluation form, although not all questions were answered by all respondents. Respondents were positive (scoring excellent, very good or good) regarding the meeting’s presenters, content, and organization. Of the 9 respondents who answered the question, 89% (8/9) noted the CUE meeting met their expectations; one individual indicated she was uncertain. Suggestions primarily focused on allocating more time for discussion.
Appendix A

CUE Annual Membership Meeting Agenda
Johns Hopkins University Carey Business School
Washington, DC
April 15, 2010; 9:00 am - 4:30 pm

9:00 am - 9:20 am Registration and continental breakfast

9:20 am - 9:45 am Welcoming remarks
Maureen Corry and John Santa, Co-chairs, CUE
Kay Dickersin and Janie Gordon, US Cochrane Center

Update on CUE activities
Maureen Corry, CUE Co-chair; Executive Director, Childbirth Connection

9:45 am - 10:15 am Keynote: Consumer engagement – Do patients engage with the healthcare system to get the care they need?
Jessie Gruman, President, Center for Advancing Health

10:15 am - 10:40 am Discussion

10:40 am - 11:00 am Break

11:00 am - 11:20 am When is RCT data sufficient to assess effectiveness and harm and when is more information needed?
Kay Dickersin, Director, US Cochrane Center

11:20 am - 11:40 am Discussion

11:40 am - 12:30 pm Introduction of member organization presentations
John Santa, CUE Co-chair; Director of the Consumer Reports Health Ratings Center, Consumers Union

12:30 pm - 1:40 pm Working lunch: Current practice of consumer involvement in systematic reviews – opportunities and challenges
Julia Kreis, Harkness/Bosch Fellow in Health Care Policy and Practice
Networking time
1:40 pm - 2:40 pm  **Workshops (Session 1)**

**Who is a consumer, and who gets to decide?**
Presenters:
Barbara Warren, CUE representative for National Coalition for LGBT Health; Director, Hunter College Institute for LGBT Social Science and Public Policy

Tom Hill, Senior Associate, Altarum Institute; Director of Programs, Faces and Voices of Recovery (effective May 2010)

**Be a peer reviewer: Learn to do a critical appraisal of a Cochrane systematic review**
Presenter:
Maryann Napoli, CUE representative and Associate Director, Center for Medical Consumers

**Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency**
Presenter:
Rachael Fleurence, Senior Research Scientist, Center for Health Economics and Policy, United BioSource Corporation

2:40 pm - 3:00 pm  **Break**

3:00 pm - 4:00 pm  **Workshops (Session 2)**
Workshops from Session 1 will be repeated.

4:00 pm - 4:30 pm  **Onward to Keystone, Colorado!**
CUE Advocacy Summit (October 17, 2010)
Joint Colloquium of the Cochrane and Campbell Collaborations (October 18 - 22, 2010)

**Evaluation**
Appendix B

CUE Annual Membership Meeting Speakers
Johns Hopkins University Carey Business School
Washington, DC
April 15, 2010; 9:00 am - 4:30 pm

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Consumers United for Evidence-based Healthcare (CUE)

Snapshot of Recent Accomplishments
Education and Training for Consumer Advocacy Groups

- *Understanding Evidence-based Healthcare: A Foundation for Action*, launched on September 15, 2007 and offered free of charge.
- Enrollment is open to any interested individual and 2,700 have enrolled in the course as of April 12, 2010.
Education and Training for Consumer Advocacy Groups

Singapore Cochrane Colloquium
October 2009

Workshop: How to ask an answerable question for health care and health research— for consumers
Education and Training for Consumer Advocacy Groups

Consumer Advocacy Summit
October 17, 2010

Cochrane and Campbell Colloquium

October 18 – 22, 2010
Keystone, Colorado
Dissemination

- CUE Annual Membership Meeting - held September 3, 2009, Washington DC and hosted by CUE and the USCC.

- USCC/CUE Webpages

- CUE Member Organization Websites, Meetings, Newsletters

- CCNet
Clearinghouse

- **Ann Fonfa (AA)**, Complementary and Integrative Medicine Stakeholder Symposium, Center for Medical Technology Policy (2009)

- **Carol Sakala (CC)**, Steering Committee member of Patient and Public Involvement Group, Guidelines International Network (G-I-N) (2009 - 2010)

- **Maureen Corry (CC) and Jennifer Sweeney (NPWF)**, Consumer participant on Patient Consumer Advisory Committee, Center for Medical Technology Policy (2009/2010)
Clearinghouse

- Terrie Cowley(TMJ), Linda Harmon (Lamaze), Carol McDaid (Faces and Voices of Recovery), Barbara Warren (National Coalition for LGBT Health) nominated to AHRQ Effective Health Care Program Stakeholder Group (2010)

- CU Representative on American Cancer Society Guidelines Panel on Practice Improvement in Cervical Screening and Management (2010)
Partnerships

- **CC, CU, NBCC, NCL, NPWF, NWHN** IOM Evidence-based Medicine Roundtable Communications Collaborative (2009 - 2010)
- **John Santa (CU)** IOM Committee on Standards for Developing Trustworthy Clinical Practice Guidelines Consumer (2009/2010)
- **Terrie Cowley (TMJA)** Patient Representative, Food and Drug Administration
Engagement: Do People Engage to Get the Care They Need?

April 15, 2010
Advances in health care simultaneously promise better outcomes while demanding more from us.
My own efforts were critical to the success of my care.
We must participate actively and knowledgeably in our care if we are to realize its benefits.
What does it take for those to find and make use of safe, decent health care?
Engagement Behaviors

= Actions individuals must take to obtain benefit of available services
Engagement Behaviors

= Actions individuals must take to obtain benefit of available services

≠ Actions of professionals or policies of institutions
Engagement Behaviors

= Actions individuals must take to obtain benefit of available services

≠ Actions of professionals or policies of institutions

≠ Compliance
APPROACH

1. 210 patient / caregiver interviews

2. Review literatures:
   a. advocacy / non-profit
   b. peer reviewed
   c. systematic reviews (Cochrane)

3. 57 key informant interviews: professionals, researchers, advocates

4. Draft EBF review by 30 stakeholders
FIND SAFE AND DECENT HEALTH CARE

COMMUNICATE WITH YOUR DOCTORS

ORGANIZE YOUR HEALTH CARE
PAY FOR YOUR HEALTH CARE

MAKE GOOD TREATMENT DECISIONS

PARTICIPATE IN YOUR TREATMENT
1. Many people do not take many of these actions.
2. Not an indictment.

Rather, a description of specific behavioral outcomes linked directly to health care and indirectly to health outcomes.
3. No one has to do all these things today.

Everyone has to do most of these things at some point.
4. *Many* of us need help to do these things.

*All* of us need to know that we are expected to do them.
Patient-centered care describes what PROVIDERS do.

EBF describes what PATIENTS must do to benefit from their care, patient-centered or not.
To the extent that primary care providers and settings help make it easier to do these behaviors, it will be patient-centered.
How big is the problem of non-participation in our health care?
Use existing government- and foundation-supported national surveys.
Dominated by questions about services received and experience of receiving them
21 national surveys, 4 regional

Identified questions to match engagement behaviors on EBF

Pulled data on each question
For the vast majority of behaviors, one third or less of respondents said that they regularly performed it.

Two thirds did it sporadically or not at all.
More likely to report having a regular doctor

Less likely to actually bring up concerns or ask questions
Less likely to act to coordinate our care

More likely to check whether our health plan will cover a specific service or test
More likely to discuss potential benefits of a test or treatment with our provider

Less likely to share in the decision-making
Less likely to follow treatment plans for non-threatening illnesses

More likely to follow treatment plan for more threatening
Less likely to do every-day health promotion

More likely to do one-shot preventive services
Less likely to use objective quality ratings

More likely to seek information to solve immediate problems
PATTERNS

1. Simpler tasks
2. Participation shallow
3. Prefer just-in-time
4. Predictable barriers don’t explain all non-participation
5. Uncertain meaning of Internet use
Are we willing to be the only health care providers about whose behavior there is so little evidence?
Our efforts are critical to the success of the health care enterprise.
When can we consider RCT data sufficient to address effectiveness and harm and when is more information needed?

Kay Dickersin
April 15, 2010
CUE Annual Meeting
Washington, DC
Steps in evidence-based healthcare

1. Frame the question
2. Find the best evidence
3. Assess the evidence
4. Apply the evidence to the individual

To understand how to recognize “best evidence” we need to understand the questions we are asking

<table>
<thead>
<tr>
<th>Question</th>
<th>Classification/Type</th>
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<tbody>
<tr>
<td>What proportion of the population is newly diagnosed with this problem each year?</td>
<td>Incidence</td>
</tr>
<tr>
<td>What proportion of the population is currently living with this problem?</td>
<td>Prevalence</td>
</tr>
<tr>
<td>What should be done to treat this problem?</td>
<td>Therapy</td>
</tr>
<tr>
<td>Will detecting this problem early, before symptoms, make a difference in my health?</td>
<td>Screening</td>
</tr>
<tr>
<td>How good is this test at detecting this problem?</td>
<td>Diagnostic Accuracy</td>
</tr>
<tr>
<td>What is the likely outcome of this problem?</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Will there be any negative effects (of an intervention)?</td>
<td>Harm</td>
</tr>
<tr>
<td>What causes this problem?</td>
<td>Etiology</td>
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<tr>
<td>How can this problem be prevented?</td>
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One size does NOT fit all! Use your question classification to seek the appropriate type of evidence

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<th>Question</th>
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<td>Incidence, prevalence</td>
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<td>Clinical trials</td>
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<tr>
<td>Screening</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>Clinical trials, cross sectional studies</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Clinical trials, followup studies</td>
</tr>
<tr>
<td>Harm</td>
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<tr>
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<td>Clinical trials, cross sectional studies</td>
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<tr>
<td>• Harm</td>
<td>Clinical trials, followup studies, case control studies</td>
</tr>
<tr>
<td>• Prevention</td>
<td>Clinical trials</td>
</tr>
</tbody>
</table>
Your questions

1. How should trial results be interpreted when the population studied is narrower than the population I am interested in (e.g., they may be all white (mammography), older, fatter, (Women’s Health Initiative) healthier)?

2. When is it ok to consider data from trials of healthy people? They may do better on the treatment and have fewer adverse events.
3. Most scientists say to watch out for subgroup analysis, yet in many cases there seems to be too much lumping and we really want to know about differences that might be present between subgroups – men and women, blacks and whites, old and young. What should we think?
Mammographic screening in women 40-49

Figure. Pooled relative risk for breast cancer mortality from mammography screening trials compared with control for women aged 39 to 49 years.

<table>
<thead>
<tr>
<th>Study/Author, Year (Reference)</th>
<th>Relative Risk for Breast Cancer Mortality (95% CrI)</th>
<th>Events/Total, n/n</th>
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<td>0.78 (0.56–1.08)</td>
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<tr>
<td>Kopparberg*/Tabar et al, 1995 (31)</td>
<td>0.72 (0.38–1.37)</td>
<td>22/9582</td>
</tr>
<tr>
<td>CNBSS-1/Miller et al, 2002 (28)</td>
<td>0.97 (0.74–1.27)</td>
<td>105/25214</td>
</tr>
<tr>
<td>Malmö/Nyström et al, 2002 (26)</td>
<td>0.73 (0.51–1.04)</td>
<td>53/13568</td>
</tr>
<tr>
<td>Stockholm/Nyström et al, 2002 (26)</td>
<td>1.47 (0.77–2.78)</td>
<td>34/14303</td>
</tr>
<tr>
<td>Östergötland*/Nyström et al, 2002 (26)</td>
<td>1.05 (0.64–1.73)</td>
<td>31/10285</td>
</tr>
<tr>
<td>Gothenburg/Bjurstam et al, 2003 (30)</td>
<td>0.70 (0.46–1.06)</td>
<td>34/11724</td>
</tr>
<tr>
<td>Age/Moss et al, 2006 (29)</td>
<td>0.83 (0.66–1.04)</td>
<td>105/53884</td>
</tr>
<tr>
<td>Total</td>
<td>0.85 (0.75–0.96)</td>
<td>448/152300</td>
</tr>
</tbody>
</table>

CNBSS-1 = Canadian National Breast Screening Study-1; CrI = credible interval; HIP = Health Insurance Plan of Greater New York.
* Swedish Two-County trial.
I ask...

- Is this population so different, is the intervention so different, is the setting so different, that I would choose to ignore these findings in favor of no evidence?
You might ask…..

• But what about observational data, can’t it be used to supplement what we know from RCTs?

• It’s complicated…..see workshop or I have slides if we have enough time.
4. How should benefits and harms be balanced when different groups assign different weights to harms (e.g., loss of fertility in women with and without kids)
Evidence-Based Healthcare

“The integration of best research evidence with clinical expertise and patient values.”

—Sackett et al, 2000
NY: Churchill Livingston
Your questions

5. How can we translate to our constituents what to look for in a trial without a lot of jargon?
Clinical Trials

Find a Clinical Trial
Search NCI's list of 8,000+ clinical trials now accepting participants.

Clinical Trial Results
Browse recent clinical trial results by type of cancer or topic

Educational Materials About Clinical Trials
Learn what clinical trials are, how they work, why they’re useful, patient care costs, and more

Noteworthy Clinical Trials
Find information about major NCI-supported clinical trials, open or closed to new participants

Conducting Clinical Trials
Find information for research teams about data and safety monitoring, online education about clinical trials, and more
Choosing to participate in a clinical trial is an important personal decision. The following frequently asked questions provide detailed information to help you, your physician, family members, or friends about deciding to join a trial. After identifying some trial options, the next step is to contact the study team for more information.

**Frequently asked questions:**

- What is a clinical trial?
- Why participate in a clinical trial?
- Who can participate in a clinical trial?
- What happens during a clinical trial?
- What is informed consent?
- What are the benefits and risks of participating in a clinical trial?
- What are side effects and adverse reactions?
- How is the safety of the participant protected?
- What should people consider before participating in a trial?
- What kind of preparation should a potential participant make for the meeting with the research coordinator or doctor?
- Does a participant continue to work with a primary health care provider while in a trial?
- Can a participant leave a clinical trial after it has begun?
- Where do the ideas for trials come from?
- Who sponsors clinical trials?
- What is a protocol?
- What is a placebo?
- What is a control or control group?
- What are the different types of clinical trials?
- What are the phases of clinical trials?
- What is an "expanded access" protocol?
6. Sometimes a trial may be well-designed in that it minimizes bias, but the comparison group is selected to make the drug or intervention look better than it really is.

7. Sometimes a statistically significant outcome is reported, but other outcomes or time points that did not show a significant difference between interventions are not reported.

How can we detect this and know when to be careful?
8. How do we interpret results from head-to-head trials (ie, 2 active interventions compared) versus results from an active intervention compared to a placebo or no intervention?
Your questions

• What is your assessment of the various adaptive designs proposed? How can advocates assess their relative merits?

• Adaptive design = changes in a trial’s design or analysis guided by looking at the trial data while the study is ongoing. Adaptive designs should ALWAYS preplan these “looks” and exactly what will be done in various circumstances.
Guidance for Industry

Adaptive Design Clinical Trials for Drugs and Biologics

DRAFT GUIDANCE
Examples of adaptive designs

Changes in:

• Study eligibility criteria
• Randomization procedure
• Treatment regimens of the different study groups (e.g., dose level, schedule, duration)
• Total sample size of the study (including early termination)
• Concomitant treatments used
• Planned schedule of patient evaluations for data collection
• Primary endpoint
• Secondary endpoints
• Analytic methods to evaluate the endpoints
Randomized controlled trials (RCT) to assess harm

- RCTs provide least biased estimates of harm:
  - Participants are randomly assigned to interventions
In patients with previously untreated metastatic clear-cell renal cell carcinoma, what is the overall toxicity of treatment with bevacizumab (Avastin) plus interferon versus interferon alone?
RCT example (cont’d)

Patients with previously untreated, metastatic clear-cell renal cell carcinoma

Random assignment of participants to groups

Bevacizumab (10 mg/kg intravenously every 2 weeks) plus interferon alpha

No toxicity

Toxicity

Interferon alpha monotherapy

No toxicity

Toxicity

Rini 2008
Limitations of RCTs

• RCTs cannot answer all questions of harm:
  – Not ethical to randomize participants to potentially harmful exposures
  – Not practical to examine harmful events that are rare or take years to manifest
Other study designs to answer questions about harm

• Cohort studies
• Case control studies
Observational cohort studies to assess harm

• Cohort studies
  – Groups of exposed and unexposed participants
    • Exposure not determined by investigators
  – Both groups followed for development of outcome
Observational cohort study example

In patients with retinal disease, what is the safety of repeat intravitreal injections of bevacizumab (Avastin), compared to repeat intravitreal injections of ranibizumab (Lucentis)?
Observational cohort study example (cont’d)

Exposed to bevacizumab

- 285 patients receiving bevacizumab injections
  - Adverse events
  - No adverse events

Exposed to ranibizumab

- 165 patients receiving ranibizumab injections
  - Adverse events
  - No adverse events

Follow up for 3-24 months
Issues in cohort studies

• Prospective and retrospective cohorts
• Appropriate for rare exposures
• May assess multiple outcomes
• Potential for bias
  – Selection bias due to non-random exposure status allocation; also if participants not at risk for developing outcome
  – Information bias if outcome assessment differs by exposure status
  – Confounding bias if groups are unbalanced with respect to other characteristics predictive of the outcome
Case control studies to assess harm

• Case control studies
  – Groups of cases and controls
  – Both groups assessed for prior exposure
Case control study example

Is there an association between development of age-related macular degeneration (AMD) and prior use of hydrochlorothiazide (HCTZ) diuretics?
Case control study example (cont’d)

Prior HCTZ use  
No prior HCTZ use

3404 persons with one or more large drusen or extensive intermediate drusen

"Cases"

Prior HCTZ use  
No prior HCTZ use

1115 persons without any large drusen and without extensive intermediate drusen

"Controls"
Issues in case control studies

• Appropriate for rare outcomes
• May assess multiple exposures
• Potential for bias
  – Selection bias if controls are not representative of those at risk for developing outcome
  – Information bias if exposure assessment differs by disease status
  – Confounding bias if groups are unbalanced with respect to other characteristics predictive of the outcome
Other study designs to assess harm

- Descriptions of individual patients (case reports) or series of patients (case series) may also be used to assess harm
  
  These study designs do not include a comparison group, so it is unknown if harmful events are related to treatment or other unidentified characteristics

- Case reports and case series may help identify questions for future research studies (generate hypotheses)
Appraising validity in studies of harm

- Were comparison groups similar?
- Were exposures and outcomes measured similarly?
- Was follow-up long enough and complete?
Were comparison groups similar?

• Minimize selection and confounding bias

• Cohort studies
  – Was the definition of exposure precise and measurable?
  – Did the investigators choose participants at risk for developing the outcome?
  – Did the investigators identify and measure potential confounding factors?
  – Were the distributions of potential confounders comparable among exposed and unexposed participants?
Were comparison groups similar? (cont’d)

• Case control studies
  – Was the definition of the outcome (case definition) precise? Were other eligibility criteria appropriate?
  – How well do controls represent the population from which cases were selected?
  – Did the investigators identify and measure potential confounding factors?
  – Were the distributions of potential confounders comparable among cases and controls?

• Residual confounding from unknown or unmeasured characteristics possible
Were exposures and outcomes measured similarly?

• Minimize information bias

• Ascertainment of *outcome* in cohort studies
  
  – Was the definition of the outcome precise and measurable?

  – Were outcome assessors masked to exposure status?

  – Was the outcome identified similarly for exposed and unexposed participants?
**Were exposures and outcomes measured similarly? (cont’d)**

- Ascertainedment of *exposure* in case control studies
  - Was the definition of the exposure precise and measurable?
  - Were interviewers/data collectors and participants masked to the study hypothesis?
  - Were interviewers/data collectors masked to disease status?
  - Was the exposure identified similarly for cases and controls?
Was follow-up long enough and complete?

• Minimize selection and confounding bias

• Cohort studies
  – Was the follow-up sufficient to identify the outcome?
  – Were attempts made to minimize loss to follow-up?
  – Did the losses differ among exposed and unexposed?
Was follow-up long enough and complete? (cont’d)

• Case control studies
  – In case of case-control studies, consider assessment of exposure rather than follow-up for outcome
  – Was the time frame of the exposure appropriate?
  – If participants were interviewed, did response rates differ among cases and controls?
  – Were there differences in availability of medical record/other data on exposure status among cases and controls?
Assessing appropriate reporting in studies of harm

Authors should follow appropriate reporting guidelines

- If study was observational (e.g., case control or cohort study)
  - STROBE guidelines should be followed

- If study was randomized clinical trials
  - CONSORT guidelines should be followed
## Examples of types of questions

<table>
<thead>
<tr>
<th>Type question</th>
<th>Example:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, prevalence</td>
<td>What is the incidence of low birth weight in minority populations compared to the white population?</td>
</tr>
<tr>
<td>Therapy</td>
<td>Is exercise effective in improving quality of life in persons with COPD?</td>
</tr>
<tr>
<td>Screening</td>
<td>Is PSA to detect prostate cancer effective in reducing mortality?</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>How effective is MRI at detecting new breast cancers in followup of women with breast cancer having lumpectomy?</td>
</tr>
<tr>
<td>Prognosis</td>
<td>What is the effect of pregnancy on exacerbating the symptoms of MS?</td>
</tr>
<tr>
<td>Harm</td>
<td>What proportion of postmenopausal women receiving Ca++/vita D can expect to have kidney stones?</td>
</tr>
<tr>
<td>Etiology</td>
<td>Is coffee consumption causally associated with developing pancreatic cancer?</td>
</tr>
</tbody>
</table>
Involving Consumers in Systematic Reviews

Julia Kreis
Harkness/Bosch Fellow
Johns Hopkins Bloomberg School of Public Health

Support for this research was provided by The Institute of Medicine and The Commonwealth Fund. The views presented here are those of the author and should not be attributed to The Institute of Medicine, The Commonwealth Fund or its respective directors, officers, or staff.
Consumer involvement is a priority for Comparative Effectiveness Research


“the CER program should fully involve consumers, patients, and caregivers in key aspects of CER, including strategic planning, priority setting, research proposal development, peer review, and disseminations”
What do we know about consumer involvement in systematic reviews?

✓ How are “consumers” defined in the literature?

✓ What is the rationale for involving consumers in health research?

✓ What are frameworks to describe consumer involvement in health research?

✓ How are consumers currently involved in systematic reviews?

✓ Which issues deserve further attention?
How are “consumers” defined in the literature?

Cochrane Glossary:
“someone who uses, is affected by, or who is entitled to use a health-related service”

CCNet:
“Consumer in Cochrane” = “an individual who has unique personal experiences that allow him or her to provide an effective healthcare user/receiver perspective to a systematic review question”

A. Herxheimer:
“informed patient who has taken the trouble to learn about research methods and can contribute insight and personal experience to trial design, or even suggest new topics for research”
What is the rationale for involving consumers in health research?

- It improves the quality of the research product.
- It is politically & ethically required.

Perspectives:

**“Consumerism”**
- Increase consumers’ satisfaction with the product.

**“Empowerment”**
- Enable consumers to greater autonomy in decision making.

Different status of consumers within a research project. Different methods for involvement.

What are frameworks to describe consumer involvement in health research?

**Consumer control**
“Consumers designing, undertaking and disseminating the results of a research project”

**Collaboration**
“Active, on-going partnership”

**Consultation**
“Asking consumers for their views and using these views to inform decision-making”

Increasing empowerment of consumers within the research process

How are consumers currently involved in systematic reviews?

Interviews with key informants
• of 15 selected organizations that conduct and/or commission systematic reviews
• in the United States
• and Campbell Collaboration, Cochrane Collaboration

Preliminary results
• Few organizations of the sample have an explicit policy to involve consumers
• No common standard of involving consumers in systematic reviews
• Different types of involvement:
  aim / groups of consumers involved / methods of involvement
Possible aims of involving consumers in systematic reviews - from the interviews -

**Quality**
- Increase the **relevance** of the review
- Increase the **accessibility** of the review

**Perception**
- Increase the **acceptance** of the review results
- Increase the **transparency, public trust and accountability** of the research process

**Cultural changes**
- Promote the **evidence-based approach**
- Establish a **culture of knowledge-exchange** between researchers and consumers
## “Personal Experience”

### Things to consider (raised by the interviewees):

- Representativeness?
- Patients or patient representatives?
- Researchers’ interest vs. patients’ interest?
## “Public Comment”

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Aim: Increase transparency, public trust and accountability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who:</td>
<td>The public</td>
</tr>
<tr>
<td>How:</td>
<td>Comment on draft protocol &amp; draft review via website</td>
</tr>
<tr>
<td>Review phase:</td>
<td>Draft protocol / draft review</td>
</tr>
<tr>
<td>Perceived impact:</td>
<td>“Safeguard” for exceptional cases</td>
</tr>
</tbody>
</table>

### Things to consider (raised by the interviewees):
- How are comments handled?
**Collaboration**

<table>
<thead>
<tr>
<th><strong>Aim:</strong></th>
<th>Increase acceptance of the review’s results and of the evidence-based approach</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who:</strong></td>
<td>Stakeholders, i.e. patient/consumer organizations</td>
</tr>
<tr>
<td><strong>How:</strong></td>
<td>Stakeholder advisory groups</td>
</tr>
<tr>
<td><strong>Review phase:</strong></td>
<td>Discuss draft protocol, draft review</td>
</tr>
<tr>
<td><strong>Perceived impact:</strong></td>
<td>Helped to increase acceptance</td>
</tr>
</tbody>
</table>

**“Stakeholder Group”**

**Things to consider (raised by the interviewees):**

- Collaboration with stakeholders vs. integrity of research?
- Person with mediating skills between researchers and stakeholders available?
What do we know about consumer involvement in systematic reviews?

- Consumers are currently involved in a variety of ways.
- These reflect different rationales for involving consumers.
- More evidence on the impact is desirable.
Which issues deserve further attention?

Issues for CUE to discuss

• **Level of involvement**
  Which level of involvement is preferred from a consumer perspective?

• **Choosing the “right” consumer organizations**
  What if a consumer organization is not dedicated to the principles of evidence-based health care?

• **Individuals or representatives**
  Should consumers be involved as individuals or as representatives of a constituency?
Thank you.

jkreis@jhsph.edu
Who Is A Consumer and Who Gets To Decide?

A Facilitated Discussion with

Barbara Warren, CUE representative for National Coalition for LGBT Health; Hunter College Institute for LGBT Social Science and Public Policy

and

Tom Hill, Senior Associate, Altarum Institute; Director Of Programs, Faces and Voices of Recovery (effective May 2010)
What does it mean to be a consumer?

- What is the difference between a consumer advocate and a consumer patient/client?
- What do the terms consumer-authenticity and lived experience mean in reference to consumer representatives?
- What considerations need to be made to help consumers gain traction in highly professionalized environments?
- How do we ensure that consumer contributions are noted, valued, and celebrated?
What support do consumer representatives need to function in their assigned roles?

- Orientation, training, mentoring
- Disclosure and safety issues
- Roles and boundaries
- Ethical issues
- Relevance, competence
- Access to resources (organizational, informational, instrumental, etc.)
- Emotional support
- Other
What are some ethical dilemmas that might arise in situations involving consumer representatives?

- Exploitation and tokenism
- Misrepresentation
- Consumer/professional relationship boundaries
- Dual or multiple roles (see two hatters)
- Disclosure and confidentiality
- Double standards (professional vs. consumer)
- Others
Two hatter: a person who qualifies and may identify as a consumer, but is also a professional in the field.

In what context would it be acceptable or optimal for a two hatter to assume a consumer role?

- Context in which no other consumers are available
- Context in which professional credibility is valued and listened to
- Context in which professional perspective will enhance or add clarity to point of view
In what context would not be advisable for a two hatter to assume a consumer role?

- Context in which professional perspective is suspect
- Context in which professional status supersedes or undermines consumer role
- Context in which professional voice overpowers consumer voice
What specific roles can a two-hatter assume when representing with other (non-two hatter) consumers?

- Organizer
- Facilitator
- Role model
- Coach or mentor
- Summarizer
- Contextualizer
What are some ethical dilemmas that might arise in situations involving consumer representatives?

- Exploitation and tokenism
- Misrepresentation
- Consumer/professional relationship boundaries
- Dual or multiple roles (see two hatters)
- Disclosure and confidentiality
- Double standards (professional vs. consumer)
- Others
“Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency”

Rachael Fleurence, PhD
Center for Health Economics and Policy
United BioSource Corporation
Workshop Objectives

• To briefly review the differences between randomized and observational evidence

• To provide practical steps to assess evidence in order to answer your key questions

• To discuss different situations that may arise (group discussion)
What does it mean to do evidence-based healthcare advocacy?

- To use the “best” evidence to advocate for interventions or strategies that are best suited to your consumers

- “Best” evidence is what we will discuss today

- How do we navigate the wealth of literature to get the best answers to the key questions of interest?
Different types of questions

• What is the diagnosis?

• What is the prognosis?

• Does the treatment work?

• Is the treatment harmful?
“I figure there's a 40% chance of showers, and a 10% chance we know what we're talking about.”
What types of evidence?

- Randomized evidence
- Observational evidence
  - Cohort studies
  - Case-control studies
  - And more…
Evidence-based medicine hierarchy

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from at least one properly randomized controlled trial.</td>
</tr>
<tr>
<td>II-1</td>
<td>Evidence obtained from well-designed controlled trials without randomization.</td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.</td>
</tr>
<tr>
<td>II-3</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.</td>
</tr>
</tbody>
</table>
Randomized evidence: an example

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women
Principal Results From the Women’s Health Initiative Randomized Controlled Trial

Writing Group for the Women’s Health Initiative Investigators

**Context** Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

**Objective** To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

**Design** Estrogen plus progestin component of the Women’s Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16,608 postmenopausal women aged 50–79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993–1998.

**Interventions** Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8,506) or placebo (n = 8,102).

**Main Outcomes Measures** The primary outcome was coronary heart disease (CHD) (myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

**Results** On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02–1.63) with 286 cases; breast cancer, 1.26 (1.00–1.59) with 290 cases; stroke, 1.41 (1.07–1.85) with 211 cases; PE, 2.13 (1.39–3.25) with 101 cases; colorectal cancer, 0.63 (0.43–0.92) with 11 cases; endometrial cancer, 0.83 (0.47–1.47) with 47 cases; hip fracture, 0.66 (0.45–0.98) with 106 cases; and death due to other causes, 0.92 (0.74–1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were: 1.22 (1.09–1.36) for total cardiovascular disease (arterial and venous disease), 1.63 (1.09–2.42) for total mortality, and 1.15 (1.03–1.28) for the global index. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10,000 person-years.

**Conclusions** Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

For editorial comment see p 366.

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(Properly) Randomized evidence is unbiased

- The internal validity of a study is defined as the extent to which the observed difference in outcomes between the two comparison groups can be attributed to the intervention rather than other factors.

- Random allocation enhances the internal validity of a study by minimizing selection bias and confounding.

- Allocation by chance in a RCT should mean that the groups being compared are similar in terms of both measured and unmeasured baseline factors.
Observational studies

- **Cohort studies**
  - Subjects are classified on the basis of the presence or absence of exposure to a particular factor and then followed for a specified period of time to determine the development of disease in each exposure group
    - E.g. The Nurses’ Health Study

- **Case-control studies**
  - A case group or series of patients who have a disease of interest and a control, or comparison, group of individuals without the disease are selected for investigation, and the proportions with the exposure of interest in each group are compared
    - E.g. Smoking and lung cancer
Myocardial infarction and stroke associated with diuretic based two drug antihypertensive regimens: population based case-control study

Inbal Boger-Agudelo, fellow trainee,1 Susan R Heckbert, professor of epidemiology,1 Noel S Weiss, professor of epidemiology,2 Barbara McKnight, professor of biostatistics,2 Curt D Furberg, professor of public health sciences,3 Kerri L Wiggins, data manager and analyst,1 Joseph A C Delaney, postdoctoral fellow,1 David S Siscovick, professor of medicine and epidemiology,1 Eric B Larson, executive director and senior investigator,1 Rozenn N Lemaire, research scientist,1 Nicholas L Smith, associate professor of epidemiology,1 Kenneth M Rice, assistant professor of biostatistics,3 Nicole L Glazer, research scientist,1 Bruce M Psaty, professor of medicine and epidemiology1

ABSTRACT
Objective To examine the association of myocardial infarction and stroke incidence with several commonly used two drug antihypertensive treatment regimens.
Design Population based case-control study.
Setting Group Health Cooperative, Seattle, WA, USA.
Participants Cases (n=153) were aged 30-79 years, had pharmacologically treated hypertension, and were diagnosed with a first fatal or non-fatal myocardial infarction or stroke between 1989 and 2005. Controls (n=952) were a random sample of Group Health members who had pharmacologically treated hypertension. We excluded individuals with heart failure, evidence of coronary heart disease, diabetes, or chronic kidney disease.
Exposures One of three common two drug combinations: diuretics plus β blockers; diuretics plus calcium channel blockers; and diuretics plus angiotensin converting enzyme inhibitors or angiotensin receptor blockers.
Main outcome measures Myocardial infarction or stroke.
Results Compared with users of diuretics plus β blockers, users of diuretics plus calcium channel blockers had an increased risk of myocardial infarction (adjusted odds ratio OR 1.98, 95% confidence interval 1.37 to 2.87) but not of stroke (OR 1.02, 95% CI 0.63 to 1.64). The risks of myocardial infarction and stroke in users of diuretics plus angiotensin converting enzyme inhibitors or angiotensin receptor blockers were slightly but not significantly lower than in users of diuretics plus β blockers (myocardial infarction: OR 0.67, 95% CI 0.52 to 1.11; stroke: OR 0.71, 95% CI 0.46 to 1.10).
Conclusions In patients with hypertension, diuretics plus calcium channel blockers were associated with a higher risk of myocardial infarction than other common two drug treatment regimens. A large trial of second line antihypertensive treatments in patients already on low dose diuretics is required to provide a solid basis for treatment recommendations.

INTRODUCTION
Untreated high blood pressure is strongly associated with myocardial infarction, stroke, and heart failure. The findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggested that low dose diuretics are superior to calcium channel blockers and angiotensin converting enzyme inhibitors as first line treatment for the prevention of one or more forms of cardiovascular disease in high risk patients with hypertension.1 A network meta-analysis confirmed and extended these findings.2

On the basis of this evidence, the seventh report guidelines issued in the United States by the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure recommend the use of low dose diuretics as first line pharmacological treatment for uncomplicated high blood pressure.3 In England and Wales, the National Institute for Health and Clinical Excellence guidelines recommend the use of low dose diuretics as the first choice therapy for high blood pressure in black patients or those aged 55 or above, and recommend a combination of diuretics plus angiotensin converting enzyme inhibitors or angiotensin receptor blockers in patients under 55 years who do not respond to initial treatment.4

About half of all patients with hypertension require a second medication to achieve control of blood pressure. In ALLHAT at five years, for instance, 40.7% of patients randomly allocated to chlorthalidone were taking at least one other antihypertensive medication. Other major classes of antihypertensive medication—β blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers—all lower blood pressure.4 5 However, the optimal second line agent for the prevention of cardiovascular disease among patients who are taking low dose diuretics and who require additional treatment for blood pressure control is not known. Although a
Observational evidence may be biased

- In observational studies, factors that determined whether a person received the intervention could result in the groups differing in factors related to the outcome either because people were preferentially selected to receive one treatment or because of choices that they made.

- The baseline differences in prognosis could confound the assessment of the effect of the intervention.
“Eating lots of fruit and vegetables may not help stave off cancer, after all”
Why?

- In the past, veggie-associated reductions of cancer-risk rates as high as 50% had been reported. But it appears that some of these early investigations may have been biased by the use of “case-control” studies.
- Such studies try to identify the factors contributing to cancer by comparing people who have the disease with those who do not, but are otherwise similar.
- The problem is that they can easily be biased if researchers do not adequately establish that the two groups being compared are, indeed, otherwise similar.
- Walter Willet, at the Harvard School of Public Health, says it appears that earlier investigations were more likely to use health-conscious people as their controls.
- These types of people are, unsurprisingly, more likely to agree to be interviewed about their health than slobby couch potatoes.

(*The Economist, April 2010*)
Evidence-based medicine hierarchy

Table 2. Hierarchy of research design

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<thead>
<tr>
<th>Level</th>
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<tr>
<td>I</td>
<td>Evidence obtained from at least one properly randomized controlled trial.</td>
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<tr>
<td>II–1</td>
<td>Evidence obtained from well-designed controlled trials without randomization.</td>
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<tr>
<td>II–2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.</td>
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<td>II–3</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.</td>
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<td>III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.</td>
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So why don’t we just use evidence based on RCTs all the time?

The problem is that in theory RCT evidence could provide answers to all our questions but in practice it is just not always available:

- When we need it
- For the population of interest (elderly, women, children, pregnant women etc.)
- For the outcome of interest (e.g. surrogate outcomes, harms, rare side effects)
How does all this help you?
Some questions that you will need to ask…

• Framing your key questions of interest:
  – What is the intervention of interest?
  – What is my population of interest?
  – What is the setting of interest?
Body of evidence vs. single studies

• To answer any question of interest, you will want to identify a body of evidence rather than a single study

• A **body of evidence** will consist of a number of studies that you will need to assess using multiple criteria

• Based on the body of evidence, you will get a sense of whether your key question is being answered, how uncertain evidence is and how likely more research is needed
Body of evidence

• How has the body of evidence been identified?
  – Was the search systematic?
  – Was the search exhaustive?
  – Was the search possibly biased?
Evaluating a body of evidence

• Three things to assess:
  – Freedom from bias (internal validity)
  – Consistency of evidence
  – Directness of evidence

• Other facets to consider:
  – Precision, dose-response association, publication bias etc.

• GRADE: Rating the quality of evidence (BMJ, 2004)
1. Freedom from bias

• Is there good internal validity?

• What was the study design?
  – If an RCT, was it well conducted? (random allocation, allocation concealment blinding, etc.) – see CONSORT
  – If an observational study, was sufficient attention given to potentially known confounders in the design and analysis? How likely are unknown confounders to be causing spurious results? – see STROBE

• What is the aggregate quality of study designs?
2. Consistency of evidence

- Consistency is the degree to which reported study effects (results) from the included studies appear to have the same direction of effect.

- Is the evidence consistent across the body of evidence?
Example of lack of consistency: HRT and CV

- For a decade organizations recommended clinicians encourage postmenopausal women to use hormone replacement therapy

- A belief that such therapy substantially decreased women’s cardiovascular risk drove this recommendation

- Had a rigorous system of rating the quality of evidence been applied at the time, it would have shown that because the data came from observational studies with INCONSISTENT results, the evidence for reduction in cardiovascular risk was of very low quality

- Ultimately, randomized controlled trials have shown that HRT fails to reduce CV risk and may even increase it
3. Directness of evidence

• Directness relates to whether the evidence links the interventions directly to the people or health outcomes of interest
  – Example 1: there may be uncertainty about the directness of the evidence if people are older, sicker or have more comorbidities than those in the studies.
  – Example 2: if one body of evidence links the intervention to surrogate or intermediate outcomes, and another body of evidence links the intermediate outcome to the most important outcomes. (e.g., statins and LDL, LDL and CV outcomes)

• Does the evidence link the interventions directly to the health outcomes?
Example of lack of directness

• The FDA licensed the antiarrhythmic agents encainide and flecainide for use in patients on the basis of drugs’ ability to reduce asymptomatic ventricular arrhythmias associated with sudden death.

• This decision failed to acknowledge that because arrhythmia reduction reflected only indirectly on the outcome of sudden death the quality of the evidence for the drugs’ benefit was of low quality.

• Subsequently, a randomized trial showed that the two drugs increase the risk of sudden death.
Final thoughts

• Critical thinking is essential to assessing the body of evidence
Group brainstorming

- How generalizable is evidence obtained from studies that did not include all the population groups?
- Is some evidence better than no evidence?
- Why do studies show different results? What if other types of evidence point in other directions?
Further reading

Textbook
• Clinical Epidemiology. Sackett et al. (1991)

Grading evidence


Guide to cohort studies
• Reader’s guide to critical appraisal of cohort studies: 1. Role and design. Rochon PA et al. BMJ. 2005 Apr 16;330(7496):895-7

Reporting randomized trials

Reporting observational studies
Contact information

• rachael.fleurence@unitedbiosource.com
Appendix I

CUE Annual Membership Meeting Evaluation Survey Instrument
Johns Hopkins University Carey Business School
Washington, DC
April 15, 2010; 9:00 am - 4:30 pm

9:20-9:45 am  Update on CUE activities

( ) Check here if you did not attend this session OR Circle the best answer for each item.

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9:45-10:15 am  Keynote: Consumer engagement – Do patients engage with the healthcare system to get the care they need?

( ) Check here if you did not attend this session OR Circle the best answer for each item.

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11:00-11:20 am  
**When can we consider RCT data sufficient to assess effectiveness and harm and when is more information needed?**

( ) Check here if you did not attend this session OR Circle the best answer for each item.

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**B. Quality of presentation by speaker**

Kay Dickersin 5 4 3 2 1

Comments: ________________________________

11:40 am-12:30 pm  
**Introduction of member organization presentations.**

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**B. Quality of presentation by speaker**

Member organizations presenting 5 4 3 2 1

Comments: ________________________________
### 12:30 -1:40 pm  Current practice of consumer involvement in systematic reviews – opportunities and challenges.

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<td>Julia Kreis</td>
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Comments: __________________________________________________________

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**Workshop:**  Who is a consumer, and who gets to decide?

I attended: ___Session 1 ___Session 2

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Comments: __________________________________________________________
### Workshop: Be a peer reviewer: Learn to do a critical appraisal of a Cochrane systematic review

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B. Quality of presentation by speaker

Maryann Napoli

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Comments:

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### Workshop: Living in a world of insufficient evidence or evidence that doesn’t appear applicable to my constituency

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Rachael Fleurence

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Comments: 
Overall Evaluation

1. The program was presented without evident commercial bias or influence.
   ( ) No
   ( ) Yes
   ( ) Not Certain

2. The program met my expectations
   ( ) No
   ( ) Yes
   ( ) Not Certain

3. Please provide comments or suggestions:

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