Systematic review and Meta analysis in Healthcare

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Outline

- Introduction
- Systematic review vs. narrative review
- The rationale for conducting a systematic review
- Steps of a systematic review
Case
A 60 year old woman with multiple myeloma is referred to a cancer center for the management of his bone disease. The attending physician wants to decide whether the patient should be treated with bisphosphonates?

Does bisphosphonates help in reducing fractures in patients with multiple myeloma?
The (conflicting) evidence!

- Randomized controlled trial 1:
  - Bisphosphonates reduce the number of vertebral fractures in patients with multiple myeloma.

- Randomized controlled trial 2:
  - Bisphosphonates have no effect on vertebral fractures and in fact bisphosphonates can lead to osteonecrosis of jaw (ONJ).
The need for research synthesis

- Health care decision makers need to access research evidence to make informed decisions for both individual patients and populations.

- There are only few important questions in health care which can be informed by consulting the result of a single empirical study.
Types of review articles

- All reviews (also called overviews)
  - Systematic reviews
  - Meta-analyses
    - Individual patient data meta-analyses
Are all reviews equal?

- In 1987, researchers examined 50 review articles published in 4 major general medical journals [Annals of Internal Med; Archives of Internal Med; JAMA; New Engl J Med]

- Findings:
  - 80% addressed a focused review question
  - 2% described the method of locating evidence
  - 2% used explicit criteria for selecting studies for inclusion
  - 2% assessed the quality of the primary studies
  - 6% performed a quantitative analysis

Are all reviews equal?

- In 1999, the survey was repeated.
- This time 158 reviews published in 6 major general medical journals [Annals of Internal Med; JAMA; New Engl J Med; BMJ; Am J Med; J of Int Med]
- Findings:
  - 34% addressed a focused review question
  - 28% described the method of locating evidence
  - 14% used explicit criteria for selecting studies for inclusion
  - 9% assessed the quality of the primary studies
  - 21% performed a quantitative analysis

McAlister et al. The medical review article revisited: has the science improved? Annals Int Med 1999;131:947-51
# Systematic vs. narrative reviews

<table>
<thead>
<tr>
<th>Core Feature</th>
<th>Narrative Review</th>
<th>Systematic Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study question</td>
<td>Often broad in scope</td>
<td>Often a focused clinical question</td>
</tr>
<tr>
<td>Data sources and search strategy</td>
<td>Which databases were searched and search strategy are not typically provided</td>
<td>Comprehensive search of many databases as well as so-called gray literature; explicit search strategy</td>
</tr>
<tr>
<td>Selection of articles for study</td>
<td>Not usually specified, potentially biased</td>
<td>Criterion-based selection, uniformly applied</td>
</tr>
<tr>
<td>Article review or appraisal</td>
<td>Variable, depending on who is conducting the review</td>
<td>Rigorous critical appraisal, typically using a data extraction form</td>
</tr>
<tr>
<td>Study quality</td>
<td>If assessed, may not use formal quality assessment</td>
<td>Some assessment of quality is almost always included as part of the data extraction process</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Often a qualitative summary</td>
<td>Quantitative summary (meta-analysis) if the data can be appropriately pooled; qualitative otherwise</td>
</tr>
<tr>
<td>Inferences</td>
<td>Sometimes evidence-based</td>
<td>Usually evidence-based</td>
</tr>
</tbody>
</table>

Courtesy: Dr. Djulbegovic
Research synthesis: systematic review and meta analysis

- **Systematic Review (SR)**
  - "The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Meta-analysis may be, but is not necessary, used as part of this process."

- **Meta-Analysis (MA)**
  - "The statistical synthesis of the data from separate but similar, i.e. comparable studies, leading to a quantitative summary of the pooled results."

Courtesy: Dr. Djulbegovic

Last JM. Dictionary of Epidemiology, 2001
The rise of SR/MA

SR/MA citations in PubMed

Publication year

<table>
<thead>
<tr>
<th>Year</th>
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SR/MA publications in 2012: World
Ethical and (regulatory) obligations

- Clinical trials should be **preceded** by a systematic review and should be reported with a **discussion** of assessing the trial’s results in the context what is already known
  - Ethical requirement for updating systematic reviews
    

- Mandating search or conduct of SR before a new clinical trial is done
  - Required in UK, Denmark, Holland
  - Peer-reviewed high impact journals require discussion of current findings in the context of a SR. (Lancet, JAMA etc.)


**Courtesy: Dr. Djulbegovic**
Case studies: rationale for SR/MA
Case Study 1: “Egg on their faces: the story of human albumin solution”*

- Human albumin solution, a blood product, has been used in the treatment of blood loss and burns since the attack on Pearl Harbour over half a century ago.
- In 1996, the global albumin market was worth $1.5 billion.

- But is human albumin administration beneficial?


Courtesy: Dr. Pai
“Egg on their faces: the story of human albumin solution”

- SR of RCTs comparing albumin with crystalloid was conducted by the Cochrane Injuries Group.
- 30 RCTs including 1,419 randomised patients identified.

- Meta-analysis showed that the risk of death among those treated with albumin was higher than in the comparison groups.
- The pooled risk ratio was 1.68 (95% CI 1.26, 2.23)

“Egg on their faces: the story of human albumin solution”

- The results were widely reported in the media and stimulated an immediate response from the regulatory agencies, the industry and the medical profession.
- The industry launched a “Albumin Support Programme” to resuscitate the ailing $1.5 billion global albumin market. The objective was to disseminate evidence supporting albumin:
  - the preparation of literature reviews supporting the use of albumin to be sent to leading regulatory authorities
  - preparation and dissemination of a Cochrane critique dossier
  - the establishment of a medical advisory panel to write articles supporting the use of albumin.
- The industry set aside $2.2 million for the program.

“Egg on their faces: the story of human albumin solution”

Case study 2: “Is passive smoking harmful?”

- A topic of great debate and controversy for many years
- First few epidemiologic studies were published in 1918
- Vigorously attacked by the tobacco industry
  - Too small an association
  - Potential bias
  - Potential confounding
  - Lack of biological proof
- Evidence accumulated over the next 2 decades
- It was not until about 15 years ago when several official bodies/agencies concluded that passive smoking is a cause of lung cancer
  - The tobacco industry continues to dispute this claim!!

“Is passive smoking harmful?”

- Hackshaw et al. conducted a SR in 1997:
  - They identified 37 published studies that reported risk of lung cancer among lifelong non-smoking women according to the husband’s smoking status.
  - Their meta-analysis revealed that the overall risk of lung cancer among lifelong non-smoking women was 1.24 times higher when their husbands smoked, as compared to those women whose husbands did not smoke.

“Is passive smoking harmful?”

Yes it is!

Case study 3: Streptokinase in acute myocardial infarction

More than 17,000 patients were treated in placebo arms from 1974 to 1988.

Streptokinase reduced mortality by 20%.

Avoidable deaths approx. 1000 patients
Steps of SR/MA
Steps of a systematic review

Research protocol
- Formulating a research question
- Search of relevant literature
- Data extraction and quality appraisal
- Synthesis (+ / - meta analysis)
- Interpretation
Protocol

Cochrane Library

- Type of SR: Intervention / diagnostic etc.
- Title
- Authors
- Background
- Objectives (research question in PICO format)
- Methods
- Criteria for considering studies for this review
  - Types of studies
  - Types of participants
  - Types of interventions
  - Types of outcome measures
- Search methods for identification of studies
- Data collection and analysis
  - Data extraction and assessment of methodological quality
- Data synthesis (meta analysis)
  - Sensitivity analysis
- Contributions of authors
- Declarations of interest
Research question

- **Patients:** patients diagnosed with multiple myeloma
- **Intervention:** bisphosphonates
- **Control:** placebo / no treatment / other bisphosphonates
- **Outcomes:** vertebral and non vertebral fractures
Search for the evidence!
Literature search

Talk to the Librarian (John). He is a very helpful guy 😊

- **Electronic databases**: Medline, Cochrane library, Embase, Lilacs etc.
- **Meeting abstracts**: ASH, ASCO etc.
- **Web**: WWW.clinicaltrials.gov

```sql
(("MultipleMyeloma"[Mesh] OR "Plasmacytoma"[Mesh] OR multiplemyeloma OR plasmacytoma OR plasmacytom* OR myelom*)
AND (bisphosphonates OR pamidronate OR zoledronate OR etidronate OR ibandronate OR clodronate OR "Clodronic Acid"[Mesh])
AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
```
Inclusion and exclusion criteria

- **Included studies:** RCTs in which interventions consist of bisphosphonates against placebo or no treatment or other bisphosphonates in multiple myeloma patients.

- **Excluded studies:** Duplicate reports, sub group analysis and studies with fewer than 10 patients.
Data extraction

- Define the outcomes *a priori*:
  - Number of participants with disease progression, time to progression, presence of pain (as defined by individual authors),
  - incidence of hypercalcemia (defined as: $=>2.65$ mmol/L),
  - adverse events (grade III/IV)

- Two review authors will extract all data, and resolve disagreements by consensus.

- After the extraction, a third review author will re-check all data.
Methodological quality assessment

- Risk of bias
- Random error
Which clinical studies are (less) biased?

1. All studies published in BMJ, Lancet, JAMA or NEJM
2. All publicly funded studies
3. All studies with more than 100 patients
4. All registered studies
5. Don’t know
Was it a fair race? Critical appraisal

**Fair start?**
Generation of sequence
Allocation concealment

Pre-specification of alpha and beta error

**Few drop outs?**
Description of drop-outs
ITT analysis

**Fair finish?**
ITT analysis
Outcome reporting bias?
Methodological quality of the included studies

Quality assessment tool for RCTs

- Assessment of risk of bias
  - Generation of randomization sequence
  - Allocation concealment
  - Description of withdrawals and drop-outs
  - Intention to treat analysis
  - Blinding methods and who were blinded

- Assessment of risk of random error
  - Pre-specification of alpha and beta error
  - A priori calculation of sample size

Newcastle Ottawa scale for observational studies
The Good The Bad The Ugly (studies)

- We need to include ALL the studies that fulfill the *a priori* set inclusion criteria. Then:
- Conduct a critical appraisal of ALL the included studies.
- We do not pick and choose..
Data extraction contd.

Method of generation of randomization sequence is considered to be:

- Adequate: if computer generation or table of random number was used;
- Unclear: not reported, or,
- Inadequate: e.g., quasi-randomized.

Allocation Concealment is considered to be:

- Adequate: if central randomization, sealed envelopes, or a code provided by a pharmacy or a company was described in the study;
- Unclear: not reported, or
- Inadequate: e.g., open table of random numbers.
# Methodological quality appraisal

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<th>Blinding?</th>
<th>Method of allocation Concealment</th>
<th>Withdrawals and drop outs</th>
<th>Intention to treat analysis</th>
<th>Randomization method</th>
<th>Adequacy of randomization method</th>
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Quantitative data synthesis

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<th>Enrolled Inn</th>
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</table>
Meta analysis is not simple addition!
## Meta analysis

<table>
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<tr>
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<th>Bisphosphonates</th>
<th>Control</th>
<th>Risk Ratio</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
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<tr>
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<td>McCloskey 2001</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<tr>
<td>Total events</td>
<td>74</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.86); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 2.97 (P = 0.003)</td>
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<td><strong>1.3.2 Pamidronate</strong></td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>232</td>
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<tr>
<td>Total events</td>
<td>46</td>
<td>68</td>
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<td>Heterogeneity: Tau² = 0.12; Chi² = 5.00, df = 2 (P = 0.08); I² = 60%</td>
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<tr>
<td>Test for overall effect: Z = 1.31 (P = 0.19)</td>
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<td><strong>1.3.3 Iblandronate</strong></td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>Total events</td>
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<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 0.18 (P = 0.86)</td>
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</table>

**Total (95% CI)**: 575 (541, 100.0%)

**Total events**: 141 (106, 100.0%)

Heterogeneity: Tau² = 0.00; Chi² = 6.42, df = 6 (P = 0.38); I² = 7%

Test for overall effect: Z = 3.27 (P = 0.001)

Favours Bisphosphonates

**Favours control**

HEALTH
Key statistical principles of meta-analysis: two stage process

Remember: the unit of analysis of a systematic review is an individual study.

- Patients in one trial are not directly compared with those in another trial
- Each trial is analysed separately
- Summary statistics are calculated for each trial
- These summary statistics are added together in the meta-analysis

Courtesy: Dr. Djulbegovic
Rationale for meta analysis is clinical not statistical

- Similar interventions for similar conditions will produce the similar effects (i.e. in the same direction) in different clinical trials
- While the effect size may not be the same, it will rarely be in the opposite directions
- However, since these are similar studies...there is potential for variation among efficacy estimates. (heterogeneity)
- If there is clinical or statistically significant heterogeneity a meta-analysis may not be valid
Heterogeneity

- Heterogeneity = The variability among studies in a systematic review

- May reflect clinical or methodological diversity or both

- How to identify heterogeneity:
  - Graphical: Do the 95%CI overlap poorly?
  - Quantification of inconsistency:
    - $I^2$ (percentage of variability in effect estimates due to heterogeneity/inconsistency rather than to chance)
      - Values > 50% may be considered to indicate substantial heterogeneity

Courtesy: Dr. Djulbegovic
Sensitivity analysis

Outcome: pain control

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
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<td>0.55 (0.30, 1.00)</td>
<td>9.9</td>
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<td>Delmas_1982</td>
<td>0.21 (0.05, 0.95)</td>
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<td>0.83 (0.64, 1.08)</td>
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<td>Daragon_1993</td>
<td>0.58 (0.26, 1.32)</td>
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<td>Menssen_2004</td>
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<tr>
<td>Subtotal</td>
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<td>94.2</td>
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<tr>
<td>doubleblindings==2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heim_1995</td>
<td>0.29 (0.12, 0.73)</td>
<td>5.2</td>
</tr>
<tr>
<td>Terpos_2000</td>
<td>0.19 (0.01, 3.76)</td>
<td>0.6</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.28 (0.12, 0.67)</td>
<td>5.8</td>
</tr>
<tr>
<td>Overall</td>
<td>0.75 (0.60, 0.95)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

test of interaction: P = 0.005
### 2.1.1 Intravenous iron

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ESA+Iron Events</th>
<th>Total</th>
<th>ESA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio (Non-event) IV, Random, 95% CI</th>
<th>Risk Ratio (Non-event) IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auerbach 2004a</td>
<td>28</td>
<td>41</td>
<td>9</td>
<td>36</td>
<td>7.8%</td>
<td>0.42 [0.26, 0.69]</td>
<td></td>
</tr>
<tr>
<td>Auerbach 2004b</td>
<td>25</td>
<td>37</td>
<td>9</td>
<td>36</td>
<td>7.6%</td>
<td>0.43 [0.26, 0.71]</td>
<td></td>
</tr>
<tr>
<td>Auerbach 2010</td>
<td>95</td>
<td>116</td>
<td>77</td>
<td>122</td>
<td>8.2%</td>
<td>0.49 [0.31, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Basit 2008</td>
<td>172</td>
<td>200</td>
<td>143</td>
<td>196</td>
<td>8.8%</td>
<td>0.52 [0.34, 0.78]</td>
<td></td>
</tr>
<tr>
<td>Beguin 2008a (1)</td>
<td>46</td>
<td>50</td>
<td>6</td>
<td>25</td>
<td>4.0%</td>
<td>0.11 [0.04, 0.28]</td>
<td></td>
</tr>
<tr>
<td>Beguin2008b</td>
<td>46</td>
<td>50</td>
<td>42</td>
<td>52</td>
<td>3.3%</td>
<td>0.42 [0.14, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Hedenus 2007</td>
<td>29</td>
<td>33</td>
<td>18</td>
<td>34</td>
<td>3.8%</td>
<td>0.26 [0.10, 0.69]</td>
<td></td>
</tr>
<tr>
<td>Henry 2007a</td>
<td>32</td>
<td>60</td>
<td>21</td>
<td>59</td>
<td>9.5%</td>
<td>0.72 [0.52, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Pedrazzoli 2008</td>
<td>56</td>
<td>73</td>
<td>47</td>
<td>76</td>
<td>7.6%</td>
<td>0.61 [0.37, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Steensma 2011a</td>
<td>112</td>
<td>164</td>
<td>106</td>
<td>163</td>
<td>9.7%</td>
<td>0.91 [0.67, 1.23]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>824</strong></td>
<td></td>
<td><strong>799</strong></td>
<td></td>
<td><strong>70.2%</strong></td>
<td><strong>0.49 [0.37, 0.66]</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Total events**: 641 / 478
- **Heterogeneity**: $\tau^2 = 0.13$, $\chi^2 = 28.63$, df = 9 ($P = 0.0007$); $I^2 = 69\%$
- **Test for overall effect**: $Z = 4.83$ ($P < 0.00001$)

### 2.1.2 Oral Iron

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ESA+Iron Events</th>
<th>Total</th>
<th>ESA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio (Non-event) IV, Random, 95% CI</th>
<th>Risk Ratio (Non-event) IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auerbach 2004c</td>
<td>15</td>
<td>43</td>
<td>9</td>
<td>36</td>
<td>9.9%</td>
<td>0.87 [0.65, 1.16]</td>
<td></td>
</tr>
<tr>
<td>Henry 2007b</td>
<td>22</td>
<td>61</td>
<td>21</td>
<td>59</td>
<td>10.1%</td>
<td>0.98 [0.76, 1.30]</td>
<td></td>
</tr>
<tr>
<td>Steensma 2011b</td>
<td>109</td>
<td>163</td>
<td>106</td>
<td>163</td>
<td>9.8%</td>
<td>0.95 [0.70, 1.28]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>267</strong></td>
<td></td>
<td><strong>258</strong></td>
<td></td>
<td><strong>29.8%</strong></td>
<td><strong>0.94 [0.80, 1.11]</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Total events**: 146 / 136
- **Heterogeneity**: $\tau^2 = 0.00$, $\chi^2 = 0.45$, df = 2 ($P = 0.80$); $I^2 = 0\%$
- **Test for overall effect**: $Z = 0.77$ ($P = 0.44$)

- **Total (95% CI)**: 1091 / 1057 / 100.0%
- **Total events**: 787 / 614
- **Heterogeneity**: $\tau^2 = 0.12$, $\chi^2 = 47.05$, df = 12 ($P < 0.00001$); $I^2 = 74\%$
- **Test for overall effect**: $Z = 4.26$ ($P < 0.0001$)
- **Test for subgroup differences**: $\chi^2 = 14.49$, df = 1 ($P = 0.0001$), $I^2 = 93.1\%$
Network meta analysis
Indirect comparisons

C = Clodronate
P = Pamidronate
I = Ibandronate

Indirect Comparisons: Vertebral fractures

- I vs C
  - Risk Ratio: 1.49 (0.82, 2.70)
- P vs C
  - Risk Ratio: 0.99 (0.57, 1.71)
- P vs I
  - Risk Ratio: 0.66 (0.32, 1.39)

Favors Bisphosphonate 1  Favors Bisphosphonate 2
Where to look for SR/MA?

- PubMed
- Cochrane Collaboration
Questions

The latest research shows that we should do something with all this research!
Thank you.

For additional questions: please send an email or call:

rmhaskar@health.usf.edu

Phone: (813) 974 9608