

# The Ethical and Methodological Challenges of Best Supportive Care Studies in Oncology

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# Aims

1. What is a “BSC study”?
2. What are the concerns about BSC studies?
3. Show me the data!
4. Are these valid approaches? Ethically? Methodologically?
5. If there are problems, so what?



# BSC Studies: Characteristics

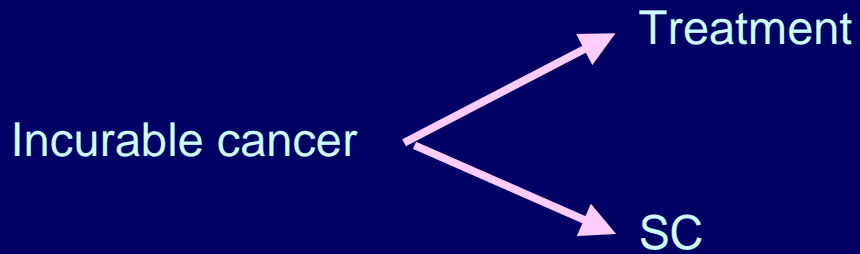
- RCTs
- Aim
  - to identify therapies that improve the duration of survival and/or the QoL over the current standard of care
  - In situations when Standard of Care is SC/PC.
- Outcomes
  - Survival
  - Quality of life
  - Both



# Design

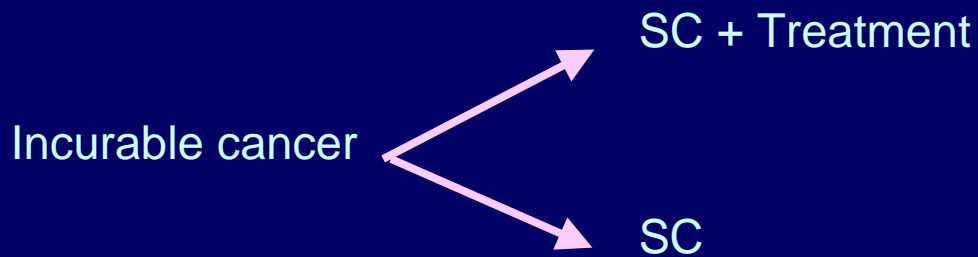
# SC

# Blinding



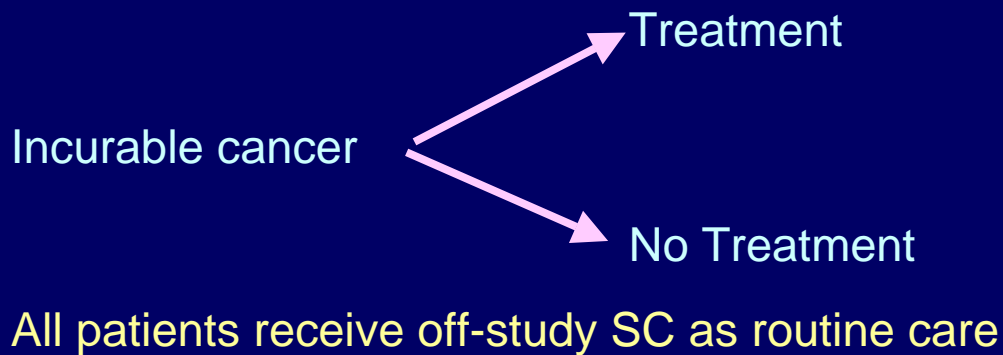
1 arm

Unblinded



2 arms

Unblinded or  
placebo blinded



Not  
evaluated

Unblinded or  
placebo blinded



# BSC studies

- 1st appear in 1980s
  - Lung cancer
  - Colorectal
  - Gastric/Esophageal cancer
  - Pancreatic/Biliary cancer



# Impact of these studies BSC studies

- Indicate that patients are generally better off getting further state of the art chemotherapy than getting ..
  - No treatment
  - “State of the art” palliative care alone
- Prominent publications: 13/50 in JCO
- Widely cited



# Criticisms

1. MacDonald N. Best supportive care. *Cancer Prev Control*. 1998 Aug;2(4):191-2.
2. Cullen M. 'Best supportive care' has had its day. *Lancet Oncol*. 2001 Mar;2(3):173-5.
3. Ahmed N, Ahmedzai S, Vora V, Hillam, Paz S. Supportive care for patients with gastrointestinal cancer. . *Cochrane Database of Systematic Reviews* 2004:Art. No.: CD003445. DOI: 10.1002/14651858.CD003445.pub2.
4. Zafar SY, Currow D, Abernethy AP. Defining best supportive care. *J Clin Oncol*. 2008 Nov 1;26(31):5139-40.



# Core Criticisms

## Standard of SC

- not consistent with any validated standard
- routine rather than best
- substandard
- delivered by physicians who were possibly inadequately skilled for the task



# Ad-hoc (routine) supportive care

Often involves:

1. inadequate evaluation of pain
  2. failure to appreciate the presence and/or severity of symptoms
  3. lack of consultation with experts in pain or palliative care
  4. sub-standard pain treatment
  5. poor symptom control
  6. lack of attention to psychological or existential distress
  7. lack of attention to family support
- Oncologists frequently feel inadequately prepared for this aspect of their work
  - Summarized in a Institute of Medicine report 1997



# Systematic Review

- 1. Describe what was done: methodology focus**
- 2. Evaluate ethical and methodological validity**
- 3. Consider implications**



# Standards of reference

- **Ethics of human research**
  - 7 universal criteria for ethical clinical research
  - Helsinki Statements
- **Methodological validity**
  - Relevant methodological items derived from CONSORT (Consolidated Standards of Reporting Trials)
  - Specifically items form complex non pharmacological interventions extension (2008)
  - Endorsed by over 200 journals and editorial groups
    - including The Lancet, BMJ, JAMA, NEJM, World Association of Medical Editors, and International Committee of Medical Journal Editors.



# Helsinki

## **WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
- 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
- 59th WMA General Assembly, Seoul, October 2008



# Helsinki: Scientific validity

## B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

- requirement that studies be predicated on a “thorough knowledge of the scientific literature”
- every version



# Helsinki: Standard of care

- Standard of care requirement for the control arm of randomized studies
- From 1975-2008: “best current care” standard
- The 2008 revision: “best current proven care”
- If there is no “best current care” or, more recently, “best current proven care” → other standards may be used if, and only if, they do not substantially increase the risk of harm to participants

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.<sup>1</sup>

# 7 Universal Criteria for Ethics in Human Studies

	Criteria	Evaluation
1	Social Value	Will this research derive knowledge or promote ends that will improve health, well being.
2	Scientific Validity	Does the research apply valid methodology to generate reliable valuable data
3	Fair subject selection	No targeting of vulnerable for risky research or favor for potentially beneficial research
4	Favorable risk benefit ratio	Minimization of risks, enhancement of potential benefits
5	Independent review	By appropriately staffed IRB
6	Informed Consent	Informing participants of risk benefit and alternatives. Voluntary decision
7	Respect for potential and enrolled participants	Permitting withdrawal, confidentiality, informing subjects of discovered benefits or risks, maintaining the welfare of participants



# The Revised CONSORT Statement for Reporting Randomized Trials: Explanation and Elaboration

Douglas G. Altman, DSc; Kenneth F. Schulz, PhD; David Moher, MSc; Matthias Egger, MD; Frank Davidoff, MD; Diana Elbourne, PhD; Peter C. Gøtzsche, MD; and Thomas Lang, MA, for the CONSORT Group

Overwhelming evidence now indicates that the quality of reporting of randomized, controlled trials (RCTs) is less than optimal. Recent methodologic analyses indicate that inadequate reporting and design are associated with biased estimates of treatment effects. Such systematic error is seriously damaging to RCTs, which boast the elimination of systematic error as their primary hallmark. Systematic error in RCTs reflects poor science, and poor science threatens proper ethical standards.

A group of scientists and editors developed the CONSORT (Consolidated Standards of Reporting Trials) statement to improve the quality of reporting of RCTs. The statement consists of a checklist and flow diagram that authors can use for reporting an RCT. Many leading medical journals and major international editorial groups have adopted the CONSORT statement. The CONSORT statement facilitates critical appraisal and interpretation of RCTs by providing guidance to authors about how to improve the

reporting of their trials.

This explanatory and elaboration document is intended to enhance the use, understanding, and dissemination of the CONSORT statement. The meaning and rationale for each checklist item are presented. For most items, at least one published example of good reporting and, where possible, references to relevant empirical studies are provided. Several examples of flow diagrams are included.

The CONSORT statement, this explanatory and elaboration document, and the associated Web site (<http://www.consort-statement.org>) should be helpful resources to improve reporting of randomized trials.

# Methods and Processes of the CONSORT Group: Example of an Extension for Trials Assessing Nonpharmacologic Treatments

Isabelle Boutron, MD, PhD; David Moher, PhD; Douglas G. Altman, DSc; Kenneth F. Schulz, PhD, MBA; and Philippe Ravaud, MD, PhD, for the CONSORT Group\*

**Background:** The conduct of randomized, controlled trials of nonpharmacologic treatments presents specific challenges that are not adequately addressed in trial reports.

**Objective:** To develop an extension of the CONSORT (Consolidated Standards of Reporting Trials) Statement for trials of nonpharmacologic treatments.

**Design:** A consensus meeting was organized to develop an extension of the CONSORT Statement that addresses randomized trials of nonpharmacologic treatments. To prepare for the meeting, a survey was conducted to identify the specific issues for discussion.

**Setting:** Consensus meeting in Paris, France.

**Participants:** A total of 33 experts attended the meeting. The experts were methodologists ( $n = 17$ ); surgeons ( $n = 6$ ); editors ( $n = 5$ ); and clinicians involved in rehabilitation ( $n = 1$ ), psychotherapy ( $n = 2$ ), education ( $n = 1$ ), and implantable devices ( $n = 1$ ).

**Measurements:** Experts indicated which of the 22 items on the CONSORT checklist should be modified or which additional items should be added specifically for nonpharmacologic treatments. During a 3-day consensus meeting, all items were discussed and ad-

ditional methodological issues related to nonpharmacologic research were identified.

**Results:** The consensus was that 11 items on the CONSORT checklist needed some modifications for nonpharmacologic trials: item 1 (title and abstract), item 3 (participants), item 4 (interventions), item 7 (sample size), item 8 (randomization), item 11 (blinding), item 12 (statistical methods), item 13 (participant flow), item 15 (baseline data), item 20 (discussion: interpretation), and item 21 (generalizability). In addition, the meeting participants added 1 item related to implementation of the intervention.

**Limitation:** Evidence was not always available to support the inclusion of each checklist item.

**Conclusion:** The methods and processes used to develop this extension could be used for other reporting guidelines. The use of this extension to the CONSORT Statement should improve the quality of reporting randomized, controlled trials assessing nonpharmacologic treatments.

*Ann Intern Med.* 2008;148:W-60-W-66.

For author affiliations, see end of text.

\*For contributors to the CONSORT Extension for Nonpharmacologic Treatment Interventions, see the **Appendix**.

www.annals.org

# Specific methodological precautions to reduce bias in non-pharmacological studies (CONSORT)

1. Credentialing of care providers and the centers in which participants were treated (Item 3)
2. Detail of the treatment components that may influence the outcome effect (Item 4a)
3. Standardization across centers (Item 4b)
4. Assessment of protocol adherence (Item 4c)
5. Acknowledgment that results may be biased by the standards of care that was actually provided (Item 20)



# BSC Literature Search



# Search Strategies

MEDLINE and CANCELRLIT searches were carried out for the period 1966-2008

- cancer (KW)/randomized (text)/ supportive (title) 100
- cancer (KW)/random allocation (KW)/supportive (text) 32
- cancer (KW)/random allocation (KW)/palliative (text) 106

146 distinct papers



# Paper selection

## Criteria

1. English language
2. Published in full
3. involved patients with advanced or metastatic cancer in which there was no standard disease modifying treatment and in which SC was the standard of care
4. investigated the use of a disease modifying treatment which was either chemotherapeutic, biologic agents, radiation, or any combination of these
5. the control arm was either SC or PC or was "no treatment" or "placebo" with SC/PC explicitly provided as off-study care

32/146 papers selected



# 2nd search (Reviews) and Hand Search

- MEDLINE and CANCELRLIT searches
  - "cancer (KW)/metastatic (any)/systematic (any)/supportive (any)/ review (any)"
  - "cancer (KW)/metastatic (any)/meta-analysis (any)/supportive (any)/ review (any)"
  - 38 papers, 16 selected for hand search
- Hand search
  - bibliographies of the systematic reviews, identified papers, and specialist texts
  - 18 additional papers that met the inclusion criterion.



# Data Extraction



# Data extraction

- 50 published papers/39 studies.
- reviewed independently by at least two researchers
- extract data regarding the study background, design, methodology, results and discussion
- The studies were classified into three groups according to their study design:
  1. treatment + SC vs. SC alone,
  2. treatment vs. SC or
  3. treatment vs. no treatment, all patients receiving off-study SC and where SC is not under evaluation



# Parameters Extracted

- Study design
- Aims
- Systematic review
- Methodological description
  - Definition SC
  - Invoked standards of SC
  - Credentialing
  - Standardization across centers
  - Application of SC
  - Patient assessments
- Reporting
  - Outcomes
  - Administration of BSC



# BSC Study Data



# Study Design, N and Endpoint

	Number of studies	N	Primary Endpoint				
			Survival	QoL	Both	symptom severity	TTP
Treatment + SC vs. SC alone	20	4628	14	2	2	1	1
Treatment vs. SC	12	1023	8		4		
Treatment vs. No treatment studies (with off-study SC)	7	1332	6		1		



# Study Design and Tumor Type

	Treatment + SC vs. SC alone	Treatment vs. SC	Treatment vs. No treatment studies (with off-study SC)	
NSCLC	10	6	4	20
Colorectal	4	1		5
Gastric/esophageal	1	2		3
Pancreatic biliary	1		2	3
Mesothelioma	2		1	3
Small cell LC	1			1
Mixed GI	1			1
Refractory Ca		1		1
Brain mets		1		1
	20	12	7	



# Treatment + BSC vs BSC (n=20)

**Study/Year**

**Ganz 1989**

**NSCLC**

**Cartei 1993**

**NSCLC**

**Helsing 1998**

**NSCLC**

**Thongprasert 1999**

**NSCLC**

**Cullen 1999**

**NSCLC**

**Roszkowski 2000**

**NSCLC**

**Anderson 2000**

**NSCLC**

**Ranson 2000**

**NSCLC**

**Spiro 2004**

**NSCLC**

**Brodowicz 2006**

**NSCLC**

**Study/Year**

**O'Brien 2006**

**SCLung**

**Muers 2008**

**mesothelioma**

**Jassem 2008**

**mesothelioma**

**Glimelius 1996**

**Pancreas or biliary**

**Glimelius 1997**

**gastric**

**Cascinu 1995**

**GI mixed**

**Scheithauer 1993**

**Colon**

**Cunningham 1998**

**Colon**

**Rao 2004**

**Colon**

**Van Cutsem 2007**

**Colon**



# Treatment vs BSC (N=12)

Rapp 1988	NSCLung
Cellerino 1991	NSCLung
Leung 1992	NSCLung
Lissoni 1992	NSCLung
ELVIS group 1999	NSCLung
Shepherd 2000	NSCLung
Murad 1993	Gastric
Pyrhonen 1995	Gastric
Mallinson 1980	Pancreas
Barni 1995	Colon
Lissoni 1994	Advanced cancer with brain metastases
Lissoni 1995	Advanced cancer



# Treatment vs No treatment (off study SC)

N=7

Huguier 2001

Pancreas

Shinchi 2002

Pancreas

O'Brien 2006

Mesothelioma

Buccheri 1989

NSCLung

Woods 1990

NSCLung

Kaasa 1991

NSCLung

Thatcher 2005

NSCLung



# Supportive Care Standards

	Reviewed contemp. SC Standards	Description of SC				Invoked Standard for SC			
		Full	Partial	Minimal	none	Ad Hoc None	Local	National	idiosync
Treatment + SC vs. SC alone (n=20)	0	1	2	15	2	10	6	3	1
Treatment vs. SC (n=12)	0			9	3	11		1 (pain + AE)	
Treatment vs. No treatment studies (with off-study SC)	NR			4	3	6	1		



# **A Randomized Trial of Alternating Chemotherapy Versus Best Supportive Care in Advanced Non-Small-Cell Lung Cancer**

By Riccardo Cellierino, Diego Tummarello, Francesco Guidi, Pierpaolo Isidori, Marzio Raspugli, Bruno Biscottini, and Giuseppe Fatati

Patients assigned to supportive care (arm B) were evaluated monthly by physical and instrumental examination in the same way as arm A.



# **Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients With Non-Small-Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy**

By Frances A. Shepherd, Janet Dancey, Rodryg Ramlau, Karin Mattson, Richard Gralla, Mark O'Rourke, Nathan Levitan, Laurent Gressot, Mark Vincent, Ronald Burkes, Susan Coughlin, Yong Kim, and Jocelyne Berille

Patients randomized to the BSC arm were treated with whichever therapy was judged to be appropriate by the treating physician. This treatment could have included treatment with antibiotics, analgesic drugs, transfusions, and palliative radiotherapy.



## Phase III Trial Comparing Supportive Care Alone With Supportive Care With Oral Topotecan in Patients With Relapsed Small-Cell Lung Cancer

*Mary E.R. O'Brien, Tudor-Eliade Ciuleanu, Hristo Tsekov, Yaroslav Shparyk, Branka Čučević, Gabor Juhasz, Nicholas Thatcher, Graham A. Ross, Graham C. Dane, and Theresa Crofts*

All patients had equal access to supportive care measures including analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, RBC transfusions, deep relaxation therapy, and palliative radiotherapy or surgical procedures.



# Methodological precautions to reduce bias (as per CONSORT)

	Credentialing SC capacity	SC includes structured symptom reporting	Standardization of BSC	Documented actual SC delivery	SC addressed in discussion or disclaimer re SC
Treatment + SC vs. SC alone (n=20)	1	3	0	4 minimal	2
Treatment vs. SC (n=12)	0	2	0	4 minimal	0
Treatment vs. No treatment studies (with off-study SC) (n=7)	0	0	0	0	1



Core Issue:

Is there a standard of care for SC?



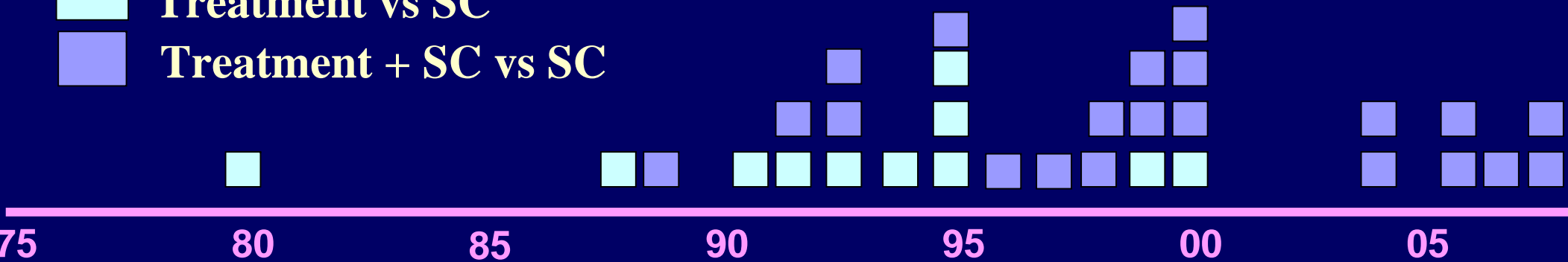
# Landmarks in the development of SC standard of care

1978	First Textbook: Saunders C. The management of terminal disease
1984	NEJM: The physician's responsibility toward hopelessly ill patients
1985	Oncology Texts incorporate PC: De Vita
1986	International cancer pain guidelines: WHO
1986-88	Specialty journals: JPSM, Pall Med, Supp Care in Cancer, J Pal Care
1990	International standards for integration of PC in oncology: WHO
1994	Multi Author Textbook of PC: OTPM
1996	PDQ supportive care guidelines
1997	Institute of Medicine Report
2004	NCCN Guidelines
2004	NICE guidelines, NIH consensus statement
2006	National Quality Forum. A Consensus Report.



# Standards of Care in SC

 Treatment vs SC  
 Treatment + SC vs SC



Single Author Textbooks and Monographs

WHO standards for cancer pain

Sections in Major Oncology texts

WHO standards for PC in Oncology

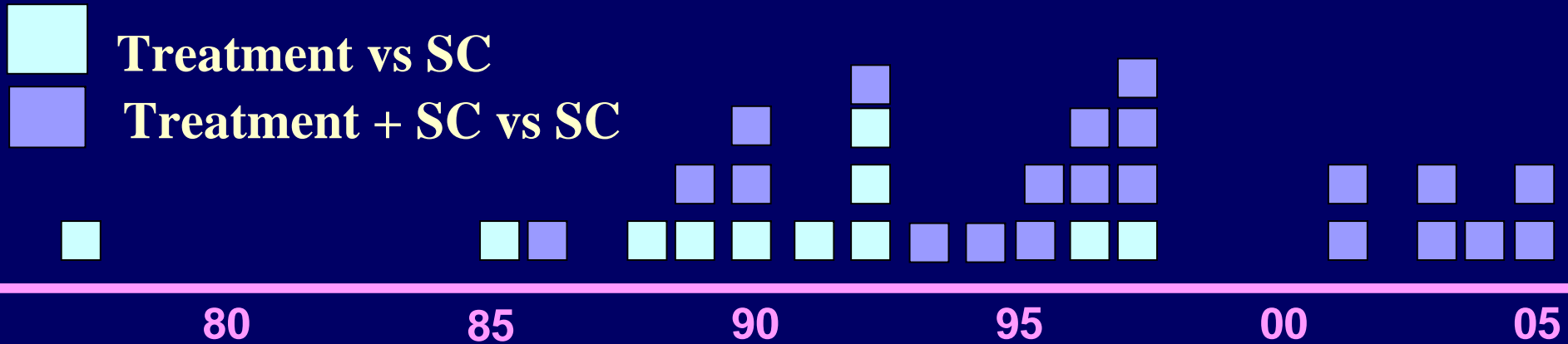
Major Multi Author Texts

National Standards

EBM standards in PC



# Standards of Care in SC



Single Author Textbooks and Monographs

WHO standards for cancer pain

Sections in Major Oncology texts

WHO standards for PC in Oncology

Major Multi Author Texts

National Standards

EBM standards in PC

Contemporaneous best practice standards existed but they were rarely reviewed, infrequently invoked or used.



# BSC content in 32 studies: the good the bad and the ugly

vinorelbine. The essential elements of ASC were defined as regular follow-up in a specialist clinic; structured physical, psychological, and social assessments at every clinic visit; rapid involvement of additional specialists; and parallel nursing support. Patients could receive, as required, steroids, analgesic drugs, appetite stimulants, bronchodilators, or palliative radiotherapy.

**Muers, Lancet 2008**

**Best supportive care was given in both groups with the same high intensity and included psychosocial support and attempts to relieve any symptoms (analgesics, antiemetic drugs, nutritional support, corticosteroids, palliative radiotherapy, surgery and so on). These principles have been outlined in a regional care programme [22].**

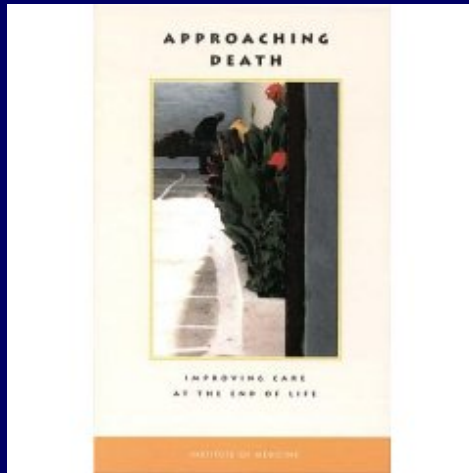
**Glimelius, Ann Onc 1996**

medication was not required. BSC was defined as the best palliative care per investigator excluding antineoplastic agents.

**Van Cutsem, JCO 2007**



# Evidence that compliance with standards improves outcomes



**Institute of Medicine Report**  
**Field MJ, Cassel EK, eds.**  
**1997.**

**NIH State-of-the-Science  
Conference  
Statement on Improving  
End-of-Life Care**  
National Institutes of Health  
State-of-the-Science Conference Statement  
December 6–8, 2004



<http://consensus.nih.gov/2004/2004EndOfLifeCareSOS024html.htm>



**Gysels M, Higginson IJ 2004:pp384.**



# Three questions

1. Are these studies compliant with the Declaration of Helsinki?
2. Are these studies scientifically valid?
3. Are these studies ethical?



# Compliance with Helsinki Accords

- Issue 1

- that studies be predicated on a “thorough knowledge of the scientific literature”

**Generally NO**

- Issue 2

- control arm requirement for “best current care”

**Generally NO**



# Methodological Validity

- None of the 32 studies with a SC control arm comply closely with the CONSORT recommended controls
  1. Almost none reviewed contemporaneous SC literature
  2. Few involved SC credentialing
  3. Few incorporated standardization
  4. None assessed adherence to standards of SC delivery.
  5. In most the description of the SC was minimal and 5 had no description.
  6. No paper clearly described the SC that was actually delivered.
  7. Only 1 offered a disclaimer that results may be influenced by the standard of SC



# Validity Treatment vs SC studies

**None since 2000**

- VERY problematic.
- The design implication
  - patients would receive one treatment or the other
  - comparison between the approaches.
- Implausibility
  - Given the symptom burden of patients and ethical imperative to relieve distress
- Data
  - None precluded symptom control from patients on the treatment arm
  - 5 studies described the provision of SC to patients on the treatment arm
  - unlikely that any patient was actually denied SC



# 7 Universal Criteria for Ethics in Human Studies

	<b>Criteria</b>	<b>Evaluation</b>
1	<b>Social Value</b>	Will this research derive knowledge or promote ends that will improve health, well being.
2	<b>Scientific Validity</b>	Does the research apply valid methodology to generate reliable valuable data
3	Fair subject selection	No targeting of vulnerable for risky research or favor for potentially beneficial research
4	<b>Favorable risk benefit ratio</b>	Minimization of risks, enhancement of potential benefits
5	Independent review	By appropriately staffed IRB
6	Informed Consent	Informing participants of risk benefit and alternatives. Voluntary decision
7	<b>Respect for potential and enrolled participants</b>	Permitting withdrawal, confidentiality, informing subjects of discovered benefits or risks, maintaining the welfare of participants



# Social Value of “BSC” control arms

## Negative social value

- Control arm of “Ad Hoc SC” with no imputed standards, implies that standards are not important.
- Giving validity to an inappropriate standard practice  
→ harm through role modeling



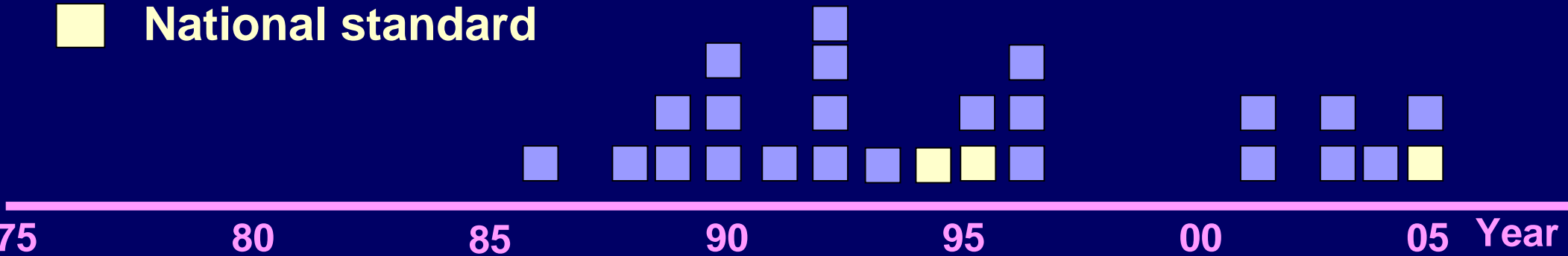
*“Experience shows that high quality health care and research go hand-in-hand. Organizations that conduct research are generally viewed as providing the best care.”*

Testimony to Senate Subcommittee on Public Health and Safety on “The Value of Clinical Research” 1997



# SC Standards of Care over time

- Ad hoc
- National standard



Single Author Textbooks and Monographs

WHO standards for cancer pain

Sections in Major Oncology texts

WHO standards for PC in Oncology

Major Multi Author Texts

National Standards

EBM standards in PC



# Scientific validity

- Not “based on a thorough knowledge of the scientific literature”
- Substandard SC may have → exaggerated benefit of intervention over non intervention arms (Straw man effect).
- Lack of of methodological precautions



# Favorable risk benefit ratio

- Clinical research can be justified only if, 3 conditions are fulfilled:
  - 1. the potential risks to individual participants are minimized,
  - 2. the potential benefits to individual participants are enhanced
  - 3. the potential benefits to individual participants and society are proportionate to—or outweigh—the risks
- Most studies did not minimize subject risk by using best contemporaneous SC practices
- Standards for SC were not reviewed, rarely invoked, and ad hoc practices were the norm.



# Respect for potential and enrolled participants

- All patients with advanced and incurable cancer are entitled to receive quality SC and PC
- Respect for the welfare → must provide adequate PC/SC
- Given the recognized deficiencies of ad hoc SC → need for recognized standards.
- In 36/39 studies this was not the case



# Conclusions

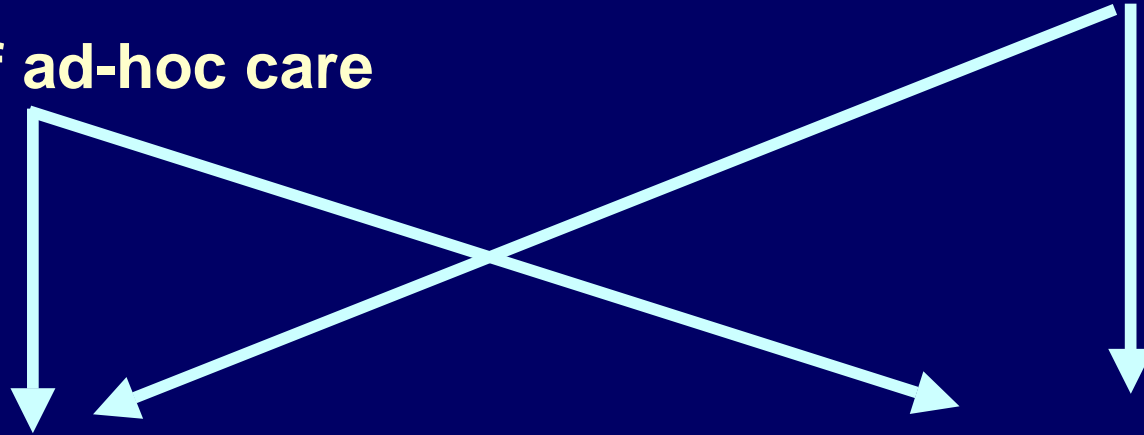
**Lack of SC standards**

**Use of ad-hoc care**

**Lack of methodologic controls**

**Substantial ethical shortcomings**

**Undisclosed potential for systematic bias**



# How did this happen?

- **Researchers**
- **IRBs**
- **Regulators**
- **Editors/Peer reviewers**



# Researchers

## ➤ Naïveté/Arrogance

- researchers unaware of standards of practice for SC or PC
- 36/39 conducted without participation of PC expert

## ➤ Deception/incentive

- Not wanting to invoke “no treatment” control arm
- SC sounds like a better more attractive option
- BEST SC!
- Cosmetic rather than real SC arm

## ➤ Can be fairly criticized for

- failing to carefully review contemporaneous standards
- Failing to involve experts in supportive or palliative care in the collaborative research process



# Institutional Review Boards (IRBs)

- Overlooked many of the ethical and methodological shortcomings of these studies.
- Reasons
  - lack of familiarity with issues specific to the SC
  - Inflated evaluation of the researchers' expertise in SC
  - lack of familiarity with the more complex methodological validity requirements of studies involving non-pharmacologic interventions.
- Not a new issue for IRBs
  - Lack the time
  - Lack research capacity,
  - Lack expertise to evaluate all of the methodologic and ethical issues raised by studies under review



# Inadequate Protection by Regulations

- Good Clinical Practice (GCP) standards
- Section 4.3 of the GCP
  - addresses standards of ancillary (off-study) care
  - very non specific
  - no reference to recognized standards of care.
- Do not ensure that patients will receive quality SC or PC



# Editors

- IRB approval and informed consent are common surrogates for Helsinki compliance
- Judgments of methodological validity are left to peer reviewers
  - familiarity with validity criteria?



# The Future of BSC



# Recommendations

- Scientific validity
  - published results should be interpreted critically
  - be aware of the potential for bias that was introduced by lax methodology.
- Ethical shortcomings
  - future studies must offer SC in accordance with contemporary evidence based standards.



# Recommendations: Study Design

- SC arm
  - Must be in both sides
  - Valid standard
  - Credentialing
  - Standardization
- “Treatment vs No treatment with off study SC”
  - Less methodologically challenging
  - If you are not studying SC, don’t make it a control arm!



# Open BSC studies

- 100+ “BSC” are currently open ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).
- Researchers and IRBs should critically review BSC studies that are currently open.
- Must review =/- amend if necessary
  - Standard of care for SC
  - Methodological safeguards as per CONSORT statement on trials of non-pharmacologic treatments
- Studies that cannot adequately address these issues should be discontinued.



# Plans

1. International initiative to define and to document standards of practice for BSC studies.
2. Development of SC/PC standards for GCP
3. Guidelines for IRB and editorial review of BSC studies



# Thanks

- Collaborators
  - Amy P Abernethy
  - Florian Strasser
  - Rama Sapir
  - S. Yousuf Zafar
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- Mentors
  - Kathy Foley, Russell Portenoy,
  - Max Schwarz, John Zalcborg
  - Tom Sandeman

