

DEVELOPMENT OF A RESEARCH AGENDA FOR

Skeletal Intervention:

PROCEEDINGS FROM A

MULTIDISCIPLINARY CONSENSUS PANEL

Kieran J. Murphy, MD – Chair

Johns Hopkins Hospital
Baltimore, MD

Dimitrios A. Kelekis, MD – Co-Chair

Eugenidion University Hospital
Athens, Greece

John Rundback, MD – Moderator

Holy Name Hospital
Teaneck, New Jersey

Thomas Faciszewski, MD

Department of Orthopaedic Spine Surgery
Marshfield Clinic
Marshfield, WI

Afshin Gangi, MD, PhD

University Hospital of Strasbourg
Strasbourg, France

Alexis D. Kelekis, MD

Eugenidion University Hospital
University of Athens
Athens, Greece

Clayton Kraft, MD

University of Bonn
Bonn, Germany

Fergus E. McKiernan, MD

Marshfield Clinic
Marshfield, WI

Daniel A. Ruefenacht, MD

Hopital Cant. Universitaire de
Geneve, Switzerland

John Shepherd, PhD

University of California at San Francisco
San Francisco, CA

Jorrit-Jan Verlaan, MD, PhD

University Medical Center
Utrecht, The Netherlands

Introduction

It has been estimated that by 2030, nearly 20% of the U.S. population will be 65 years of age or older and as a result medical and public attention will gravitate towards the diseases affecting the older population and the minimally invasive procedures that can be utilized to treat them (1). Osteoporosis is a serious public health threat for an estimated 44 million Americans, or 55 percent of the people 50 years of age and older (2).

Osteoporosis, a debilitating disease characterized by low bone mass and structural deterioration of bone tissue, can lead to bone fragility and an increased susceptibility to fractures (3). In the U.S., 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis (4). The majority of the annual 1.5 million osteoporosis related fractures are located in the spinal region, including about 700,000 vertebral fractures (5-8).

Vertebroplasty and kyphoplasty are minimally invasive procedures that can be utilized in the treatment of painful osteoporotic vertebral compression fractures.

Vertebroplasty, is a minimally invasive image guided treatment performed mainly by interventional radiologists but also by orthopaedic surgeons/neurosurgeons. It stabilizes the collapsed vertebra with the injection of polymeric bone cement into the spine.

Kyphoplasty is a procedure that involves inserting a small balloon into the collapsed vertebra. The balloon is inflated to compress the bone peripherally creating a cavity, and then cement is injected into the resulting void. Vertebroplasty and kyphoplasty are popular procedures in the United States, with up to 50,000-150,000 procedures being performed each year, a figure that continues to follow a positive trend (Arthrocare,

Kyphon industry estimates). Globally, approximately 7,400 physicians are trained to perform these procedures, enabling an international network to exchange data and best practices.

Even though the vast majority of vertebroplasty and kyphoplasty cases concern osteoporotic compression fractures, people with malignant disease are excellent candidates for these minimally invasive procedures. In Europe, 80% of vertebroplasties are used in the treatment of pain for malignant compression fractures. Data suggest that vertebroplasty can significantly alleviate pain associated with malignant compression fractures (9). While more evidence based studies with larger populations need to be conducted, results thus far demonstrate the broad applicability of vertebroplasty and kyphoplasty procedures in this area.

There is a growing body of clinical evidence from 17 years of experience that these procedures are effective treatments but there are weaknesses in the peer reviewed vertebroplasty and kyphoplasty scientific literature since only a few studies achieve level one evidence by Cochrane review/analysis (10). Most of the reports have been retrospective. These gaps in the scientific literature have brought into question the efficacy and benefit of minimally invasive skeletal intervention procedures.

Meeting Organization

To identify current needs and strategic focuses for Skeletal Intervention (SI) research, a multidisciplinary meeting of prominent SI experts was convened in September 2005 by the Cooperative Alliance for Interventional Radiology Research (CAIRR), the clinical trials network of the Society of Interventional Radiology Foundation, in partnership with the Cardiovascular and Interventional Radiology Society of Europe

Foundation (CIRSE Foundation). The purpose of the meeting was to establish a prioritized research agenda for SI that includes basic science/technology research, pilot clinical studies, and pivotal clinical trials.

CAIRR and its CIRSE partners, assembled an international panel of experts in the area of SI to address the research needs related to this important and emerging global healthcare concern. The research consensus panel (RCP) was charged with identifying gaps in the scientific literature in the area of SI and suggesting priority areas or studies that could be undertaken to address these pressing areas.

A 10-member SI RCP was created from a list of leading scientists developed by the SI RCP Chair, CAIRR Advisory Council, and the CIRSE Foundation Board of Directors. The Panel included members from interventional radiology (six), orthopedics (three), internal medicine (one), and physics (one). Representatives from industry were invited to be present at the meeting and were provided the opportunity to participate in the RCP proceedings by asking questions and providing their input on the ranking of the priorities that were identified by the Panel.

Before the meeting, the members of the RCP were given an agenda describing the structure and intent of the session. The meeting was structured into four parts per standard CAIRR RCP process: 1) introductory presentations; 2) moderated roundtable Panel discussion with comments from industry and governmental representatives; 3) research topic prioritization; and 4) preliminary clinical research protocol development. Oral presentations provided a summary of the previously reported outcomes from research involving SI therapies. These presentations included findings of Epidemiology of Osteoporosis (FM), Bone architecture: Implications for intervention (JV), Medical

Therapy of Osteoporosis (FM), Kyphoplasty (TF), Vertebroplasty (KM), Percutaneous disc interventions (AK), Skeletal Pain Management (AK), Ablative and other therapies for skeletal malignancy (AG), and Skeletal imaging (JS). The key aspects of these presentations are summarized in the results of rank order prioritization of participant responses of this manuscript.

Data Collection and Analysis

The Panelists' comments were compiled into a list of proposed SI research topics. Each Panel member and industry attendee was asked to prioritize the topics from each composite list with a scoring system used in previous CAIRR RCPs (11).

The scores assigned by the expert panelists were summated to yield a total priority score for each topic. Many of the topics were similar in essential content, and thus were collapsed into broader, all encompassing categories. The collapsed categories were circulated to the panelists along with the original categories to ensure that the essential meaning and intent of the initial categories had been retained in the collapsed categories. The aggregate rank score for each topic was then re-calculated. The same process was performed by the industry representatives.

The feasibility and design of a pivotal trial to address the single highest priority clinical research topic identified by the RCP were discussed in detail.

Panel Presentations

Select panel members were asked to present on empirical research in their area of expertise. These presentations aimed to educate all panel and audience members on the most vital topics facing SI research, and to create dialogue among the panelists.

Kyphoplasty and Vertebroplasty

The increasing trend of kyphoplasty and vertebroplasty procedures has enabled academic research centers to perform in-depth studies on the effectiveness of these procedures *versus* conservative management. Every study to date has found that and vertebroplasty both techniques provide substantial pain relief in osteoporotic vertebral compression fractures (regardless of height restoration) and predictable functional restoration (5-8).

Future studies and registries involving kyphoplasty and vertebroplasty should strive to provide further data that may provide insight to many questions that are still outstanding in this expanding field. Ultimately, physicians need to know when to use these techniques, as current indications and exact working mechanisms are not clearly defined and/or understood. Further scientific evidence is needed to identify how much restoration of strength and shape of the vertebral body is needed for a beneficial effect without increasing the risk of adjacent fracture as a result of decreased bone elasticity at the augmented level. Questions also remain about the long term effects of PMMA cement on the surrounding bone architecture. PMMA particles resulting from many loadcycles of the augmented vertebral body may cause osteolysis leading to further vertebral body collapse. Furthermore, PMMA cement obstruction of nutritional pathways to the disc may be a concern for the long term health status of intervertebral discs in younger patients. It was suggested that performing a clinical trial, using the absolute minimum injection of 1-2 ml of cement *versus* the current volume of 4-8 ml cement typically used today, could provide important information to determine the lowest effective volume possibly leading to less cement leakage related complications. In order to provide data to answer many clinical questions, the need for a long term prospective randomized trial

medical/vertebroplasty/kyphoplasty study was recognized, although it was also acknowledged that conducting such a trial has been difficult due to low study enrollment.

Percutaneous disc interventions

Studies in this growing area have also revealed that it is important to define which type of percutaneous technique should be used according to specific indications. The non-controlled published series are variable in technique, indication and outcome assessment and susceptible to investigator and patient bias (in a condition that has a predominantly subjective outcome. The Cochrane systematic review of the treatment of lumbar disc herniation, that takes into account the quality as well as the quantity of published evidence, concluded that “There is moderate evidence that automated percutaneous discectomy produces poorer clinical outcomes than standard discectomy or chymopapain” (9)

Skeletal Pain Management

A Johns Hopkins evaluation of 205 consecutive percutaneous vertebroplasty procedures found that 44% of patients had a complete improvement of pain, 46% reported significant pain improvement, 5% reported minimal improvement, 5% reported that their pain level was unchanged, and no patients reported increased pain after undergoing a percutaneous vertebroplasty procedure. The patient pool included 86% who were osteoporotic, and 12% who were neoplastic. Parameters of the study excluded prospective patients who had coagulopathy or an infection, but did not place limits on age, height or elapsed time from the fracture. Patients included in the study had to have to exhibit pain resistance to medical management (10).

Dual X-Ray Bone densitometry.

A study of visual assessment of vertebral fracture using lateral dual X-ray absorptiometry scan found that vertebral fracture assessment showed good sensitivity (>80%) in identifying moderate/severe deformities and excellent negative predictive value (>90%) in distinguishing subjects without from those with vertebral deformities on a per subject basis. Subjects included 80 postmenopausal women (28 osteoporotic, 40 osteopenic), aged 61 to 84 years. A comparison of VFA results to radiography found that of 987 non-fractured vertebral bodies evaluated by lateral vertebral assessment (LVA), the densitometrists correctly identified 960 as normal. Only 2.8% were incorrectly classified as fractured. All but one (94%) of grade 2 or 3 fractures were correctly identified using LVA. Of 22 grade 1 compression fractures present in evaluable vertebral bodies, 11 were detected by LVA. Through continued research, this type of assessment may further exhibit its benefits in the clinical evaluation of patients at risk of osteoporosis, or during the clinical study patient selection period.(12).

Ablative and other therapies for skeletal malignancy

The preferred method for relieving cancer pain associated with spinal metastases is to eliminate the tumor(s). When percutaneous procedures are elected to treat spinal tumors, interventional radiologists choose among available therapeutic modalities, which are classified in three categories: cementoplasty, radiofrequency (RF) ablation, and cementoplasty combined with RF ablation. For spinal and acetabular metastases, cementoplasty is the preferred technique. In case of large invasion of soft tissue surrounding the vertebral body, or acetabulum, RF ablation can be combined with vertebroplasty. RF ablation is an excellent alternative to painful osteolytic bone

metastases, in part because single or few localizations are required during the procedure. In addition, RF ablation is able to produce a much more predictable tumor destruction than injection of alcohol. While RF ablation can be an effective treatment, it does not come without limitations. The monopolar technique is contraindicated if the lesion is too close to neurological structures or sensitive organs, such as the colon or intestine. In these cases, the bipolar technique can be used for a precise limitation of the coagulation.

Panel Discussion

During the panel discussion, there was considerable interest in vertebroplasty, kyphoplasty, disease information and the development and utility of outcome databases. Specifically, there was consensus that comparison of the benefits and risks associated with vertebroplasty and kyphoplasty should be documented through a data collection registry. Developing a central databank where researchers are able to submit their outcomes would be of benefit to the field of spinal intervention through data analysis and dissemination of best practices. Additionally, large quantities of data on vertebroplasty and kyphoplasty therapies could be utilized to develop inclusion criteria and comment on the current state of outcomes assessment. Discussion also focused on additional benefits of informatics, including the possibility of marketing an established database and its findings to both industry and insurance companies. Primarily, a large database of qualitative and quantitative information regarding spinal intervention outcomes would enable physicians, particularly those who are at smaller practices and do not have the benefit of a robust research institution, to easily reference best practices when faced with the predicament of deciding on the best course of treatment for patients with specific symptoms.

Results of Rank Order Prioritization of Participant Responses

A total of 60 clinical research topics were initially proposed as areas needing additional investigation. After aggregate grouping, 19 clinical research topics were obtained. The results of the voting on the aggregate clinical SI research topics are presented in **Table 1** (preliminary voting – prior to collapsing categories) and **Table 2** (priority voting – subsequent vote on collapsed categories). Representatives from industry were also invited to vote on the clinical topics; priority voting results are presented in **Table 3**.

After preliminary voting, "Develop registry, collecting data from vertebroplasty, medical therapy and kyphoplasty practitioners -- develop uniform criteria for inclusion and reporting and outcomes assessment" was identified as the highest priority area for clinical investigation. This topic received a total score of 31 and was selected as an important potential research area by five of ten panelists. Additionally, this area was scored as the "highest priority" research area by one panelist. The next highest ranked clinical research area was "tackle daily practice issues in osteoporosis -- plan and execute early intervention trial of vertebroplasty vs. non-operative care, within two to four weeks of occurrence, allow cross-over of non-operative care patients at one week." This area also received a total score of 28 and was selected as a potential research area by four of the ten panelists. Additionally, this area was scored as the "highest priority" research area by three panelists.

Also receiving a total score of 28 was "Develop informatics structure for integrating information on disease management and outcomes -- market this database

type of research to industry and payers. Database should include imaging as well as other outcome data". This area was selected as a potential research area by four of the ten panelists and was scored as the "highest priority" research area by two panelists.

From these data it was determined that, because no single clinical research area received the simple majority in the number of panelists voting for the priority and that because there were three priority areas that received similar total scores as well as top priority rankings, a secondary consensus process was needed. The panelists felt that the informatics component did not represent a clinical trial design per se, but could be structurally incorporated into a pivotal trial's methodology. The registry issue has been independently identified as an important component for ongoing data collection regarding patterns of care and broad based clinical outcomes, and is the focus of other initiatives. However, registries do not have the scientific integrity of RCTs and do not provide the Level 1 evidence sought by CAIRR facilitated clinical research trials.

This discussion resulted in a comprehensive review and recategorization of all identified research areas. The new categorization was approved by the RCP chair and subsequent consensus was reached by the panel on the new categories through a modified Delphi technique (21). This process required each panel member to review the new priority list to ensure that all of the initial priorities were accurately reflected in the new categorization. This was done before any additional evaluation of the topics to ensure that the panelists agreed that the new categories captured the intent of the initial responses provided at the meeting.

Panelists were asked to review the categories and provide their impression of how well the new categories maintained the essential meaning and intent of the initial

responses. Each category was scored from 1 – lowest score to 5 – highest score.

Following consensus on the new categories all panelists were asked to rank the new 19 category areas in order from 1-highest priority to 19-lowest priority. Somewhere in the text the reader should learn the level of panelist participation. Were there 10 of 10 responders for all questions?

In the priority voting system utilized, a lower score is a higher priority. In this process all panelists were required to rank each priority area. The recategorization and priority ranking process identified "prospective randomized study of intervention vs. medical management for osteoporotic compression fracture, with crossover to intervention for those who fail medical therapy" as the highest priority area for clinical investigation. This priority area received a total score of 22, and was scored as the "highest priority" research area by 3 panelists. The next highest clinical research priority area was "prospective randomized trial of vertebroplasty vs. kyphoplasty for osteoporosis vertebral compression fractures." This area received a total score of 36. This area was scored as the "highest priority" research area by 2 panelists.

Through this process the SI RCP members were able to identify two high priority clinical study areas and three additional study areas that need further investigation to add meaningful information on important unanswered clinical questions relating to SI.

Discussion: Advancing SI Research

The first step in the CAIRR process for any important research area is the development of a multidisciplinary RCP to identify and prioritize those research projects which are pivotal, feasible, translational, innovative, and strategic. The work product of each RCP is expected to include a white paper summarizing the consensus strategic

research agenda, an executive protocol summary for clinical trial development, and a list of basic science and clinical research priorities to guide development of RFAs within the SIR Foundation and other organizations.

The possibility that different choices in panelist selection or topic grouping would have altered the priority rankings of some research topics must be considered. However, given the general concordance of the Panelist rankings, it appears unlikely that the subjective decisions made in grouping topics fundamentally altered the RCPs major conclusions.

The priority areas identified and scored by the Panel show many important clinical research questions remain unanswered in the area of SI. For most SIR and CIRSE members, these spine interventions will represent growth areas. The final rankings reported by this Panel show potential areas for future research consideration. As such, they are intended to provide a framework to stimulate progress in several areas: 1) establishment of multidisciplinary working groups to begin further critical research discussions and protocol development to address some of the SI research questions identified by the RCP; 2) engage the U.S. Food and Drug Administration and National Institutes of Health in the study design and funding of SI related clinical studies; 3) appropriation of resources within foundation's and other funding organizations for SI grant development and clinical trial execution; and 4) development of SIR Foundation RFAs and other mechanisms with which to stimulate new clinical and basic science research in this important area.

The Panel considers a prospective randomized controlled study of intervention *versus* medical management for osteoporotic compression fracture, with crossover to

intervention for those who fail medical therapy to represent the most important clinical SI research priority. Additionally, there is a need for level 1 scientific evaluation of the role of vertebroplasty and kyphoplasty in acute osteoporotic compression fractures.

A prospective randomized study of intervention vs. medical management for osteoporotic compression fracture, with crossover to intervention for those who fail medical therapy, will provide a structure to analyze procedures that individual practitioners themselves are currently unable to do. Results disseminated from a multi-center study that assesses intervention and medical therapy will help provide treatment answers that will benefit all physicians who treat patients with this painful condition that will ultimately facilitate the quality of clinical practice. Additionally, results from a comprehensive and well-conducted clinical trial will address the need for scientific data that is being requested by national and international insurance and payer organizations. The development of this trial could allow for increased information exchange, across borders, (*i.e.*, sharing of study protocols and case report forms that could be modular and applicable to all future spine intervention investigations).

Summary

A multidisciplinary spine intervention research consensus panel was convened to develop a prioritized research agenda for skeletal intervention. The Panel recommended that the priority clinical research area was to develop a prospective randomized study of interventional therapy *versus* medical management for osteoporotic compression fracture, with crossover to intervention for those who fail medical therapy. Accordingly, the research needs identified by the skeletal intervention research consensus panel will be a

subject of multidisciplinary trial development efforts facilitated by CAIRR in the years ahead.

References

1. Nussbaum et al. "A Review of Complications Associated with Vertebroplasty and Kyphoplasty as Reported to the Food and Drug Administration Medical Device Related Web Site."
2. Percutaneous vertebroplasty and kyphoplasty vertebral body fractures in cancer patients
3. Blue Cross Blue Shield. (2003). "BCBS Percutaneous Vertebroplasty Technology Evaluation Center SIR Study Review."
4. Fourney, D., Schomer, D., Chlan-Fourney, J., Suki, D., Rhines, K., and Gokaslan, K. 2004 Oncology RCP, 2005 Venous RCP, 2005 Reflux RCP.
5. Kanis JA. Epidemiology of osteoporosis. *Bone* 1992; 13 (Suppl. 1):7–15.
6. Lieberman IH, Dudeney S, Reinhardt MK, Bell G. Initial outcome and efficacy of "kyphoplasty" in the treatment of painful osteoporotic vertebral compression fractures. *Spine* 2001;26.
7. Kasperk C ,et al, Treatment of painful fractures by kyphoplasty in patients with primary osteoporosis: A prospective nonrandomized controlled study. *J Bone Min Res* 2005;
8. Feltes C, et al, Immediate and early postoperative pain relief after kyphoplasty without significant restoration of vertebral body height in acute osteoporotic vertebral fractures. *Neurosurg Focus* 2005;18 (Comment- you've chosen 3 KP trials but fewer PV trials. This might be construed to impart a bias. My personal recommendation would be to avoid cherry-picking one trial over another and use the MCAC publication to refer to KP and PV more generically)
9. Haines SJ., Jordan N., Boen JR., Nyman JA., Oldridge NB., Lindgren BR. "Discectomy strategies for lumbar disc herniation:results of the LAPDOG trial". *Journal of Clinical Neuroscience* (2002) 9(4), 411,417.
10. Gibson JNA, Grant IC, Waddell G. Surgery for lumbar disc prolapse (Cochrane Review). In: *The Cochrane Library*, Issue 3. Oxford, Update Software, 2001.
11. Cristiana Vasconcelos, Philippe Gailloud, Norman J. Beauchamp, Donald V. Heck, and Kieran J. Murphy. **Is Percutaneous Vertebroplasty without Pretreatment Venography Safe? Evaluation of 205 Consecutive Procedures** *AJNR Am J Neuroradiol* 2002 23: 913-917.

12. [Visual Assessment of Vertebral Deformity by X-ray Absorptiometry: A Highly Predictive Method to Exclude Vertebral Deformity](#) J. Rea et al *Osteoporos Int.* 2000.
13. Department of Health and Human Services Administration on Aging
<http://www.aoa.gov/prof/Statistics/statistics.asp>
14. National Osteoporosis Foundation
<http://www.nof.org/osteoporosis/diseasefacts.htm>
15. Hochmuth et al, "Percutaneous bertebroplasty in the therapy of oseoporotic vertebral compression fractures: a critical review." 2006
16. Melton LJ, Frye MA, Wahner HW, Riggs BL (1989) Epidemiology of vertebral fractures in women. *American Journal of Epidemiology*, 129:1000–1011
17. Kanis JA. Epidemiology of osteoporosis. *Bone* 1992; 13 (Suppl. 1):7–15.
18. Ettinger MP. Aging bone and osteoporosis: strategies for preventing fractures in the elderly; *Arch Intern Med.* 2003 Oct 13; 163(18) 2237–2246
19. McGraw JK, Barr JD, Mathis JM, Sacks D. Society of Interventional Radiology Quality Improvement Guidelines for Percutaneous Vertebroplasty. *J Vasc Interv Radiol* 2003; 14:827–831
20. Zoarski GH, Olan WJ, Stallmeyer MJ, Dick BW, Deyne M. Percutaneous vertebroplasty for osteoporotic compressionfractures: quantitative prospective evaluation of long-term outcomes. *J Vasc Interv Radiol* 2002; 13:139–148
21. <http://www.is.njit.edu/pubs/delphibook>

Table 1. SI - Clinical Topics (Panelists) Need to make clear the distinction between “Number of Panelists” in each of the Tables. Providing an “n” for each table might help.

<u>Topic Number</u>	<u>Topic</u>	<u>Score</u>	<u>Number of Panelists</u>	<u>Ranking</u>
1	Develop registry, collecting data from vertebroplasty, medical rx and kyphoplasty practitioners -- develop uniform criteria for inclusion and reporting and outcomes assessment	31	5	1
2	Develop informatics structure for integrating information on disease management and outcomes -- market this database type of research to industry and payers. Database should include imaging as well as other outcome data	28	4	2
3	tackle daily practice issues in osteoporosis -- plan and execute early intervention trial of vertebroplasty vs. non-operative care, within 2-4 wks of fx occurrence, allow x-over of non-op pts at 1 week	28	4	2
4	prospective randomized trial of vertebroplasty for kyphoplasty	22	4	4
5	Study the natural history of early osteoporotic VCF's -- study numerous outcomes	22	4	4
6	vertebroplasty vs. XRT for malig dz	19	3	6
7	Basic science -- cement is extremely important, need to motivate industry to help determine what are the implications of cement on osteolysis, particle effects over time as bony morphology changes	15	3	7

8	Minimal access surgery -- very focused single level degenerative lumbar disease management looking at, for example, everything from laser to focused RF	14	2	8
<u>Topic Number</u>	<u>Topic</u>	<u>Score</u>	<u>Number of Panelists</u>	<u>Ranking</u>
9	Need to educate the public and other practitioners that patients don't have to have pain: need marketing	14	4	8
10	Develop algorithms for evaluation of patients with spinal disease	13	3	10
11	Very important to bring clarity to vertebroplasty vs. kyphoplasty -- need prospective and multicenter trials to determine inclusion/exclusion of pts	13	3	10
12	Post mortem micro-CT and micro-MR to look at interface between cement and bone, bone structural analysis, etc	13	3	10
13	The most important in the beginning is information; need to educate all specialties of the difference between normal therapies and osteoplastic therapies (bone injections)	12	2	13
14	Study differences in treatment patterns and outcomes in different regions	8	2	14
15	Create strategy for promoting value of database research	8	2	14
16	Support the development of Interventional Spine Therapist as unique practitioner	8	2	14
17	examine biopsy material of patients who have undergone vertebroplasty	7	1	17

18	Would not randomize patients with late fractures, but randomize of patients with fx's of <3-4 wks is mandated	7	1	17
19	Basic Science --- inject two vertebral bodies and look at effect on intervening disc	7	3	17
<u>Topic Number</u>	<u>Topic</u>	<u>Score</u>	<u>Number of Panelists</u>	<u>Ranking</u>
20	determine effects on spinal column and vertebral augmentation of therapies -- from outcome as well as economic aspect	7	1	17
21	Organizational -- collaborate with multiple centers and trials, multispecialty	7	1	17
22	For short and long term outcomes -- quantitative vertebral morphometry to quantify fx risk and state of the spine, bone mineral density assessment using DXA of lumbar spine to reference treated population to reference population, QCT of adjacent vertebral bodies to look at BMD as a result of stress changes after treatment at other levels, use finite element analysis of QCT data	6	2	22
23	Studies of spinal interventions need to assess dynamic changes as component of height restoration	6	2	22
24	Assess 3D morphology/volume of the implant and effect on outcomes as well as changes over time	5	1	24
25	study why the procedure works -- do sham vs. active treatment series -- mainly osteoporotic VCF's	5	1	24
26	Study kyphoplasty to decompress fresh traumatic fractures within 72 hours of injury	5	1	24

27	Biomechanical evaluation, in sense of the posture of the patient. Look at vertebral angulation as part of study, effect of treatment on the way the patient stands and walks and other physiatriac parameters	5	1	24
28	Develop screening programs for osteoporotic spinal disease	5	1	24
<u>Topic Number</u>	<u>Topic</u>	<u>Score</u>	<u>Number of Panelists</u>	<u>Ranking</u>
29	Converge medical imaging technology and treatment strategies -- study role of imaging to direct and determine therapy	5	1	24
30	Develop portfolio of clinical trials addressing different questions -- provide universal tools and structure and study design elements to be used across all trials -- allow experts to stay in their areas of strength working within centralized cooperative group	5	1	24
31	Work with outside vendor to develop multinstitutional and multinational database using normalized data (harmonize dataset), including rotational 3D imaging	5	1	24
32	Study prophylactic vertebro/kyphoplasty	4	2	32
33	Focus on treatment of osteoporotic VCF -- are we being overagressive?	3	1	33
34	The second problem is the implant, the cement -- collaborate with industry to develop new cements	3	1	33
35	Basic science -- perform postmortem histologic evaluations of patients treated with spinal interventions	3	3	33

36	Consider further study of disc disease -- single level disc disease non-operative vs. operative rx	3	1	33
37	Study capability of rotational 3D angiography to analyze spinal disease	3	1	33
<u>Topic Number</u>	<u>Topic</u>	<u>Score</u>	<u>Number of Panelists</u>	<u>Ranking</u>
38	Stress importance to industry of multidisciplinary research -- create strategic and research alliance focused on spine problems	3	1	33
39	Evaluate MR imaging before and after spinal treatments, including contrast enhanced, diffusion/perfusion MR	3	1	33
40	Need to study DDD Rx as additive to vertebral intervention	3	1	33
41	Look at economic impact of treatment for spinal dz and disc dz	2	2	41
42	Disseminate information regarding spinal interventions	1	1	42
43	Early intervention trial -- prospective study with cross-over arm			
44	RCT of percut disc intervention vs. discectomy			
45	evaluate natural history of osteoporotic fractures			
46	assess vertebral body characteristics and other factors affecting timing of intervention			
47	There are different referral biases in US and EU (70% malig in EU, 30-50% in US); need study of osteoporotic fx cement augmentation vs. medical disease			
48	vertebroplasty vs. medical mgmt for benign dz with crossover			

- 49 vertebroplasty vs. RFA for metastatic bone dz
- 50 Would be very hard to ascribe to randomized trial (would place rx of malig dz at 50%) -- oncologists would not accept this
- 51 Test new implants as they are developed -- panel should provide corporate advisory function
- 52 In Switzerland, 20% of health care money is for Rx of LBP -- should work to study benefit of interventions in this population

<u>Topic Number</u>	<u>Topic</u>	<u>Score</u>	<u>Number of Panelists</u>	<u>Ranking</u>
53	Develop informatics structure for integrating information on disease management and outcomes -- market this database type of research to industry and payors. Database should include imaging as well as other outcome data			
54	Develop informatics structure for integrating information on disease management and outcomes -- market this database type of research to industry and payors. Database should include imaging as well as other outcome data			
55	The basis of the problem is the randomized trial -- this is the first step to be accepted by everyone. Study whether fracture can be stopped or reversed after treatments.			
56	Difficult to recruit fresh fractures for randomized trial -- thought is that current guidelines are to wait 3 weeks -- need to reexamine and perhaps change guidelines			

- 57 Organizational issue -- need to centrally analyze and provide QA for standardization and cross-calibration
- 58 Study local delivery of HMG-coA reductase inhibitors in clinical use (RFP)
- 59 Need to address back pain rather than spine dz
- 60 Precision assessment of implant volume as a subset

Table 2. SI – Priority Clinical Topics (Panelists)

<u>Ranking</u>	<u>Topic</u>	<u>Score</u>	<u>Number of Panelists</u>	<u>Number of Votes for Top Ranking</u>
1	Prospective randomized study of Intervention vs. medical management for osteoporotic compression fracture, with crossover to intervention for those who fail medical therapy	22	8	3
2	Vertebroplasty vs. kyphoplasty for osteoporotic VCFs	36	8	2
3	Biomechanical/postural cohort study pre-and post-intervention assessment	59	8	
4	Early intervention trial – Randomized controlled trial of patients with VCFs < 4 weeks old, with crossover	60	8	2
5	Develop broad treatment outcomes registry/database utilizing uniform criteria, inclusion/exclusion, reporting (normalized data)	62	8	1
6	Vertebroplasty vs. RFA for malignant VCFs	87	8	
7	Patterns of care study evaluating outcomes and diagnostic algorithms in patients with osteoporotic VCFs	89	8	
8	XRT vs. vertebroplasty for malignant VCFs	89	8	
9	Study sham vs. active treatment for osteoporotic VCFs	91	8	1
10	Clinical trial evaluating spinal canal and vertebral augmentation	96	8	

11	VCF imaging study or database - QCT, MRI, DXA	96	8
12	Cost effectiveness trial	97	8
13	Study fracture reversal/arrest after therapy	100	8
14	Natural history study of osteoporotic VCFs	104	8
15	Very early intervention trial of kyphoplasty within 72 hours of injury	106	8
16	Disc intervention trial	107	8
17	Prophylactic intervention trial	123	8
18	LBP treatment trial, combining therapies of DDD and VCF	140	8
19	Intravertebral HMG-CoA reductase inhibitor trial	155	8

Table 3. SI – Priority Clinical Topics (Industry)

Topic Number	Clinical Topics	Score	Top Priority
1	Prophylactic intervention trial	29	4
2	Vertebroplasty vs RFA for malignant VCFs	30	
3	Study fracture reversal/arrest after therapy	40	
4	Disc intervention trial	41	
5	Develop broad treatment outcomes registry/database utilizing uniform criteria, inclusion/exclusion, reporting (normalized data)	47	
6	Early intervention trial - RTC of patients with VCFs < 4 weeks old, with crossover	55	
7	Intervention vs medical management for osteoporosis, with crossover	56	2
8	XRT vs vertebroplasty for malignant VCFs	56	
9	Cost effectiveness trial	63	1
10	Patterns of care study evaluating outcomes and diagnostic algorithms in patients with osteoporotic VCFs	65	
11	Vertebroplasty vs kyphoplasty for osteoporotic VCFs	70	
12	Clinical trial evaluating spinal canal and vertebral augmentation	76	
13	Biomechanical/postural cohort study pre-and post-intervention assessment	84	
14	VCF imaging study or database - QCT, MRI, DXA	86	
15	LBP treatment trial, combining therapies of DDD and VCF	87	
16	Very early intervention trial of kyphoplasty within 72 hours of injury	97	
17	Natural history study of osteoporotic VCFs	99	
18	Study sham vs active treatment for osteoporotic VCFs	121	
19	Intravertebral HMG-CoA reductase inhibitor trial	128	