**Long-term outcomes with spinal versus general anesthesia for hip fracture surgery**

Emily A. Vail; Rui Feng; Frederick Sieber; Jeffrey L. Carson; Susan S. Ellenberg; Jay Magaziner; Derek Dillane; Edward R. Marcantonio; Daniel I. Sessler; Sabry Ayad; Trevor Stone; Steven Papp; Derek Donegan; Samir Mehta; Eric S. Schwenk; Mitchell Marshall; J. Douglas Jaffe; Charles Luke; Balram Sharma; Syed Azim; Robert Hymes; Ki-Jinn Chin; Richard Sheppard; Barry Perlman; Joshua Sappenfield; Ellen Hauck; Ann Tierney; Annamarie D. Horan; Mark D. Neuman; on behalf of the REGAIN (Regional versus General for Promoting Independence after Hip Fracture) Investigators

**Appendix**

**Table of Contents**

[Collaborating investigators by role: REGAIN Investigators Group 2](#_Toc145595270)

[Appendix Figure 1. CONSORT diagram 5](#_Toc145595271)

[Appendix Table 1. Recorded patient outcomes by follow-up period 6](#_Toc145595272)

[Appendix Table 2. Sensitivity analysis. Hazard ratio for death at day 365 between spinal versus general anesthesia among patients 85 years of age or older, adjusted for time-treatment interaction 7](#_Toc145595273)

[Appendix Table 4. Median 12-item WHODAS 2.0 scores between groups at 60, 180, and 365 days 8](#_Toc145595274)

[Appendix Table 5. Site-reported adverse events, by treatment arm, grouped by Medical Dictionary for Regulatory Activities System Organ Class 9](#_Toc145595275)

[Appendix Table 6. Comparison of trial participant characteristics with- and without- missing vital status data at 365 days after randomization 10](#_Toc145595276)

1

# Collaborating investigators by role: REGAIN Investigators Group

**Writing Committee:** Emily Vail, Susan Ellenberg, Annamarie Horan, Ann Tierney, Rui Feng, Mark Neuman.

**Collaborators:** Thomas Looke, Sandra Bent, Ariana Franco-Mora, Pamela Hedrick, Matthew Newbern (Advent Health); Rafik Tadros, Karen Pealer (Allegheny and Forbes Hospital); Kamen Vlassakov, Carolyn Buckley, Lauren Gavin, Svetlana Gorbatov, James Gosnell, Talora Steen, Avery Vafai, Jose Zeballos (Brigham & Women’s Hospital); Jennifer Hruslinski (Center for Advocacy for the Rights and Interests of the Elderly); Louis Cardenas, Ashley Berry, John Getchell, Nicholas Quercetti (Christiana Hospital); Manal Hassan, Gauasan Bajracharya, Damien Billow, Michael Bloomfield, Evis Cuko, Mehrun K. Elyaderani, Robert Hampton, Hooman Honar, Dilara Khoshknabi, Daniel Kim, David Krahe, Michael M. Lew, Conjeevram B. Maheshwer, Azfar Niazi, Partha Saha, Ahmed Salih, Robert J. de Swart, Andrew Volio (Cleveland Clinic); Kelly Bolkus, Matthew DeAngelis, Gregory Dodson, Jeffrey Gerritsen, Brian McEniry, Ludmil Mitrev (Cooper University Hospital); M. Kwesi Kwofie, Anne Belliveau, Flynn Bonazza, Vera Lloyd, Izabela Panek (Dalhousie University); Jared Dabiri, Chris Chavez, Jason Craig, Todd Davidson, Chad Dietrichs, Cheryl Fleetwood, Mike Foley, Chris Getto, Susie Hailes, Sarah Hermes, Andy Hooper, Greg Koener, Kate Kohls, Leslie Law, Adam Lipp, Allison Losey, William Nelson, Mario Nieto, Pam Rogers, Steve Rutman, Garrett Scales, Barbara Sebastian, Tom Stanciu (Dell Seton Medical Center at the University of Texas); Gregg Lobel, Michelle Giampiccolo, Dara Herman, Margit Kaufman, Bryan Murphy, Clara Pau, Thomas Puzio, Marlene Veselsky (Englewood Hospital and Medical Center); Kelly Apostle, Dory Boyer, Brenda Chen Fan, Susan Lee, Mike Lemke, Richard Merchant, Farhad Moola, Kyrsten Payne, Bertrand Perey, Darius Viskontas (Fraser Health); Mark Poler (Geisinger Medical Center); Patricia D’Antonio, Greg O’Neill (Gerontological Society of America); Amer Abdullah, Jamie Fish-Fuhrmann (Hartford Hospital); Mark Giska, Christina Fidkowski, Stuart Trent Guthrie, William Hakeos, Lillian Hayes, Joseph Hoegler, Katherine Nowak (Henry Ford Hospital); Jeffery Beck, Jaslynn Cuff, Greg Gaski, Sharon Haaser, Michael Holzman, A. Stephen Malekzadeh, Lolita Ramsey, Jeff Schulman, Cary Schwartzbach (Inova Fairfax Medical Center); Tangwan Azefor, Arman Davani, Mahmood Jaberi, Courtney Masear (Johns Hopkins Bayview Medical Center); Syed Basit Haider, Carolyn Chungu, Ali Ebrahimi, Karim Fikry, Andrew Marcantonio, Anitha Shelvan (Lahey Hospital and Medical Center); David Sanders, Collin Clarke, Abdel Lawendy (London Health Sciences Center); Gary Schwartz, Mohit Garg, Joseph Kim (Maimonides Medical Center); Juan Caruci, Ekow Commeh, Randy Cuevas, Germaine Cuff, Lola Franco, David Furgiuele (New York University Langone Medical Center); Matthew Giuca, Melissa Allman, Omid Barzideh, James Cossaro, Armando D'Arduini, Anita Farhi, Jason Gould, John Kafel, Anuj Patel, Abraham Peller, Hadas Reshef, Mohammed Safur, Fiore Toscano (New York University- Winthrop Hospital); Tiffany Tedore, Michael Akerman, Eric Brumberger, Sunday Clark, Rachel Friedlander, Anita Jegarl, Joseph Lane, John P. Lyden, Nili Mehta, Matthew T. Murrell, Nathan Painter, William Ricci, Kaitlyn Sbrollini, Rahul Sharma, Peter A.D. Steel, Michele Steinkamp, Roniel Weinberg, David Stephenson Wellman (NewYork-Presbyterian Hospital – Weill Cornell Medicine); Antoun Nader, Paul Fitzgerald, Michaela Ritz (Northwestern Memorial Hospital); Greg Bryson, Alexandra Craig, Cassandra Farhat, Braden Gammon, Wade Gofton, Nicole Harris, Karl Lalonde, Allan Liew, Bradley Meulenkamp, Kendra Sonnenburg, Eugene Wai, Geoffrey Wilkin (Ottawa Hospital); Karen Troxell, Mary Ellen Alderfer, Jason Brannen, Christopher Cupitt, Stacy Gerhart, Renee McLin, Julie Sheidy, Katherine Yurick (Reading Hospital); Fei Chen, Karen Dragert, Geza Kiss, Halina Malveaux, Deborah McCloskey, Scott Mellender, Sagar S. Mungekar, Helaine Noveck, Carlos Sagebien (Rutgers-Robert Wood Johnson University Hospital); Luat Biby, Gail McKelvy, Anna Richards (Peace Health Sacred Heart Medical Center at Riverbend); Ramon Abola, Brittney Ayala, Darcy Halper, Ana Mavarez, Sabeen Rizwan (Stony Brook Medicine); Stephen Choi, Imad Awad, Brendan Flynn, Patrick Henry, Richard Jenkinson, Lilia Kaustov, Elizabeth Lappin, Paul McHardy, Amara Singh (Sunnybrook Health Sciences Center); Joanne Donnelly, Meera Gonzalez, Christopher Haydel, Jon Livelsberger, Theresa Pazionis, Bridget Slattery, Maritza Vazquez-Trejo (Temple University Hospital); Jaime Baratta, Michael Cirullo, Brittany Deiling, Laura Deschamps, Michael Glick, Daniel Katz, James Krieg, Jennifer Lessin, Jeffrey Mojica, Marc Torjman (Thomas Jefferson University Hospitals); Rongyu Jin, Mary

Jane Salpeter (Toronto Western Hospital); Mark Powell, Jeffrey Simmons, Prentiss Lawson, Promil Kukreja, Shanna Graves, Adam Sturdivant, Ayesha Bryant, Sandra Joyce Crump (University of Alabama Birmingham Medical Center); Michelle Verrier, James Green, Matthew Menon (University of Alberta); Richard Applegate, Ana Arias, Natasha Pineiro, Jeffrey Uppington, Phillip Wolinsky (University of California Davis Medical Center); Amy Gunnett, Jennifer Hagen, Sara Harris, Kevin Hollen, Brian Holloway, Mary Beth Horodyski, Trevor Pogue, Ramachandran Ramani, Cameron Smith, Anna Woods (University of Florida College of Medicine); Matthew Warrick, Kelly Flynn, Paul Mongan (University of Florida Jacksonville); Yatish Ranganath, Sean Fernholz, Esperanza Ingersoll-Weng, Anil Marian, Melinda Seering, Zita Sibenaller, Lori Stout, Allison Wagner, Alicia Walter, Cynthia Wong (University of Iowa Hospitals & Clinics); Denise Orwig (University of Maryland); Maithri Goud, Chris Helker, Lydia Mezenghie, Brittany Montgomery, Peter Preston,

J. Sanford Schwartz, Ramona Weber, Lee A. Fleisher, Samir Mehta, Alisa J. Stephens-Shields, Cassandra Dinh, Aron Schwartz (University of Pennsylvania/Penn Presbyterian Medical Center); Jacques E. Chelly, Shiv Goel, Wende Goncz, Touichi Kawabe, Sharad Khetarpal, Amy Monroe, Vladislav Shick (University of Pittsburgh Medical Center); Max Breidenstein, Timothy Dominick, Alexander Friend, Donald Mathews (University of Vermont Medical Center); Richard Lennertz, Robert Sanders, Helen Akere, Tyler Balweg, Amber Bo, Christopher Doro, David Goodspeed, Gerald Lang, Maggie Parker, Amy Rettammel, Mary Roth, Marissa White, Paul Whiting (University of Wisconsin-Madison); Brian F.S. Allen, Tracie Baker, Debra Craven, Matt McEvoy, Teresa Turnbo (Vanderbilt University Medical Center); Stephen Kates, Melanie Morgan, Teresa Willoughby (Virginia Commonwealth University Medical Center); Wade Weigel, David Auyong, Ellie Fox, Tina Welsh (Virginia Mason Medical Center); Bruce Cusson, Sean Dobson, Christopher Edwards, Lynette Harris, Daryl Henshaw, Kathleen Johnson, Glen McKinney, Scott Miller, Jon Reynolds, B. Scott Segal, Jimmy Turner, David VanEenenaam, Robert Weller (Wake Forest Baptist Medical Center); Jineli Lei, Miriam Treggiari, Shamsuddin Akhtar, Marcelle Blessing, Chanel Johnson, Michael Kampp, Kimberly Kunze, Mary O'Connor (Yale-New Haven Hospital).

**Executive Committee:** Mark D. Neuman (Chair), Jeffrey Carson, Susan Ellenberg, Lakisha J. Gaskins, Jay Magaziner, Frederick Sieber

**Recruiting Site Leads :** Thomas Looke (Advent Health); Rafik Tadros (Allegheny and Forbes Hospital); Kamen Vlassakov (Brigham & Women’s Hospital); Louis Cardenas (Christiana Hospital); Daniel I. Sessler (Cleveland Clinic Main Campus); Sabry Ayad (Cleveland Clinic Fairview); Manal Hassan (Cleveland Clinic Hillcrest); Kelly Bolkus; Ludmil Mitrev (Cooper University Hospital); M. Kwesi Kwofie (Dalhousie University); Jared Dabiri (Dell Seton Medical Center at the University of Texas); Gregg Lobel (Englewood Hospital and Medical Center); Trevor Stone (Fraser Health); Mark Poler (Geisinger Medical Center); Richard Sheppard (Hartford Hospital); Mark Giska (Henry Ford Hospital); Robert Hymes (Inova Fairfax Medical Center); Frederick Sieber (Johns Hopkins Bayview Medical Center); Balram Sharma (Lahey Hospital and Medical Center); David Sanders (London Health Sciences Center); Gary Schwartz (Maimonides Medical Center); Mitchell Marshall (New York University Langone Medical Center); Matthew Giuca (New York University-Winthrop Hospital); Tiffany Tedore (NewYork-Presbyterian Hospital – Weill Cornell Medicine); Antoun Nader (Northwestern Memorial Hospital); Stephen Papp, Greg Bryson (Ottawa Hospital); Karen Troxell (Reading Hospital); Jeffrey Carson, Geza Kiss (Rutgers-Robert Wood Johnson University Hospital); Barry Perlman (Peace Health Sacred Heart Medical Center at Riverbend); Syed Azim (Stony Brook Medicine); Stephen Choi (Sunnybrook Health Sciences Center); Ellen Hauck (Temple University Hospital); Eric Schwenk (Thomas Jefferson University Hospitals); Ki Jinn Chin (Toronto Western Hospital); Mark Powell (University of Alabama Birmingham Medical Center); Derek Dillane (University of Alberta); Richard Applegate (University of California Davis Medical Center); Joshua Sappenfield (University of Florida College of Medicine); Matthew Warrick (University of Florida Jacksonville); Yatish Ranganath (University of Iowa Hospitals & Clinics); Derek Donegan, Nabil Elkassabany, Mark Neuman (Penn Presbyterian Medical Center); Jacques E. Chelly, Charles Luke (University of Pittsburgh Medical Center); Mark A. Hoeft (University of Vermont Medical Center); Richard Lennertz, Robert Sanders (University of Wisconsin-Madison); Brian F.S. Allen (Vanderbilt

University Medical Center); Stephen Kates (Virginia Commonwealth University Medical Center); Wade Weigel (Virginia Mason Medical Center); J. Douglas Jaffe (Wake Forest Baptist Medical Center); Jinlei Li (Yale-New Haven Hospital)

**Data and Safety Monitoring Board:** Duminda N. Wijeysundera (Chair), Sachin Kheterpal, Reneé H. Moore, Alexander K. Smith, Laura L. Tosi

**Publications and Ancillary Studies Committee:** Mark D. Neuman (Chair), Jeffrey Carson, Derek Dillane, Susan Ellenberg, Nabil Elkassabany, Rui Feng, Robert A. Hymes, Thomas Looke, Jay Magaziner, Diane Menio, Daniel Sessler, Frederick Sieber

**Adverse Event Monitoring Committee:** Samir Mehta (Chair), Jeffrey Carson, Annamarie Horan, Lee Fleisher

**Patient Engagement Committee:** Mark D. Neuman (Co-Chair), Diane Menio (Co-Chair), Jennifer Hruslinski, Robert A. Hymes, J. Douglas Jaffe, Lolita Ramsey, Lakisha J. Gaskins, Christine Langlois

**Site Monitoring Team:** Lakisha J. Gaskins (Lead), Lydia Mezenghie, Brittany Montgomery, Samuel Oduwole, Thomas Rose

# Appendix Figure 1. CONSORT diagram



|  | *All participants (N=1,599)* |
| --- | --- |
|  | *60 Day(31-90 day window)* | *180 Day(135-225 day window)* | *365 Day(305-425 day window)* |
| *Status* | *No. (%)* | *No. (%)* | *No. (%)* |
| Died by mid-window | 63 (3.9) | 132 (8.3) | 190 (11.9) |
| Interview completed | 1,381 (86.4) | 1,269 (79.4) | 1,170 (73.2) |
| Known alive at start of window (walking status unknown) | 112 (7.0) | 111 (6.9) | 67 (4.2) |
| Withdrawn prior to window (vital status unknown) | 23 (1.4) | 39 (2.4) | 62 (3.9) |
| Unknown | 20 (1.3) | 48 (3.0) | 110 (6.9) |
| Appendix Table 1. Recorded patient outcomes by follow-up period  |

*Hazard ratio for death at day 365, spinal versus general*

*anesthesia 95% CI*

2.59a 0.25 - 27.1

a. Cox proportional hazards model adjusted for sex, fracture type, country, and a time-treatment interaction.

# Appendix Table 2. Sensitivity analysis. Hazard ratio for death at day 365 between spinal versus general anesthesia among patients 85 years of age or older, adjusted for time-treatment interaction

6

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Day after trial enrollment* | *Randomized to* *spinal anesthesia* | *Randomized to* *general anesthesia* |
|  |  |  *Number of patients* | *No. (%)* | *Number of patients* | *No. (%)* |
| *Able to walk without human assistance* | Day 60 | 628 | 551 (87.7) | 649 | 574 (88.4) |
| Day 180 | 600 | 542 (90.3) | 621 | 561 (90.3) |
| Day 365 | 586 | 519 (88.6) | 584 | 530 (90.8) |
|  |
| **Appendix Table 3.** Recovery of independence in ambulation over time within the overall study sample |

|  |  |  |
| --- | --- | --- |
|  | *Randomized to spinal anesthesia* | *Randomized to general anesthesia* |
| *Days after trial enrollment* | *No.* | *Median WHODAS**2.0 score (IQR)* | *No.* | *Median WHODAS 2.0 score (IQR)* |
| 60 | 225 | 22.7 (8.3, 43.2) | 241 | 18.2 (6.3, 31.8) |
| 180 | 249 | 10.4 (2.3, 27.1) | 274 | 10.4 (2.1, 27.3) |
| 365 | 280 | 10.4 (2.1, 29.2) | 276 | 8.3 (0.0, 22.9) |
| IQR: interquartile range, WHODAS: 12-item World Health Organization Disability Schedule 2.0 scale; scores range from 0 to 100, with lower scores indicating lower degrees of disability.  |
| Appendix Table 4. Median 12-item WHODAS 2.0 scores between groups at 60, 180, and 365 days |

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Spinal N=795** |  | **General N=805** |
|  | **Severity gradea** |  | **Severity gradea** |
| **System organ class** | **1** | **2** | **3** | **4** | **5** | **All grades** |  | **1** | **2** | **3** | **4** | **5** | **All grades** |
| Blood and lymphatic system disorders | 33 | 26 | 79 | 1 | 0 | 139 |  | 35 | 30 | 79 | 0 | 0 | 144 |
| Cardiac disorders | 13 | 29 | 18 | 5 | 5 | 70 |  | 7 | 15 | 7 | 10 | 7 | 46 |
| Gastrointestinal disorders | 35 | 24 | 17 | 3 | 4 | 83 |  | 51 | 27 | 16 | 3 | 0 | 97 |
| General disorders and administration siteconditions | 36 | 33 | 14 | 0 | 63 | 146 |  | 39 | 22 | 6 | 1 | 68 | 136 |
| Infections and infestations | 23 | 30 | 35 | 5 | 5 | 98 |  | 14 | 38 | 24 | 4 | 1 | 81 |
| Injury, poisoning andproceduralcomplications | 20 | 26 | 28 | 2 | 2 | 78 |  | 29 | 24 | 40 | 4 | 2 | 99 |
| Metabolism and nutrition disorders | 31 | 15 | 17 | 3 | 1 | 67 |  | 27 | 12 | 16 | 5 | 1 | 61 |
| Nervous system disorders | 28 | 24 | 19 | 2 | 5 | 78 |  | 22 | 18 | 13 | 1 | 2 | 56 |
| Psychiatric disorders | 22 | 21 | 7 | 1 | 0 | 51 |  | 24 | 23 | 23 | 1 | 0 | 71 |
| Renal andurinary disorders | 16 | 20 | 3 | 3 | 1 | 43 |  | 16 | 25 | 4 | 1 | 1 | 47 |
| Respiratory, thoracic and mediastinal disorders | 17 | 19 | 16 | 5 | 2 | 59 |  | 27 | 18 | 24 | 6 | 7 | 82 |
| Surgical and medical procedures | 27 | 35 | 16 | 1 | 0 | 79 |  | 24 | 38 | 23 | 1 | 0 | 86 |
| Vascular disorders | 15 | 25 | 24 | 1 | 2 | 67 |  | 14 | 15 | 15 | 2 | 2 | 48 |
| Other organ systemsb | 23 | 27 | 15 | 2 | 0 | 67 |  | 26 | 19 | 16 | 1 | 1 | 63 |
| Totals | 339 | 354 | 308 | 34 | 90 | 1125 |  | 355 | 324 | 306 | 40 | 92 | 1117 |

aSeverity grades range from 1 (mild) to 5 (death). bIncludes congenital, familial, and genetic disorders; eye

disorders; hepatobiliary disorders; investigations; musculoskeletal and connective tissue disorders; neoplasms, benign, malignant, and unspecified; reproductive system and breast disorders. All events with a listed start date through post randomization day 365 are shown. Where subjects had more than one event reported within a given grade, all reported

 events are included.

# Appendix Table 5. Site-reported adverse events, by treatment arm, grouped by Medical Dictionary for Regulatory Activities System Organ Class

9

|  |  |
| --- | --- |
|  | *Vital status at or beyond 365 day interview after randomization* |
|  | **Known No. = 1427** | **Unknown No. = 172** |
| Randomized to general anesthesia | 713/1427 (50.0) | 91/172 (52.9) |
| Randomized to spinal anesthesia | 714/1427 (50.0) | 81/172 (47.1) |
| Age at randomization, years |  |  |
| <65 | 187/1427 (13.1) | 25/171 (14.6) |
| 65-74 | 329/1427 (23.1) | 55/171 (32.2) |
| 75-84 | 476/1427 (33.4) | 52/171 (30.4) |
| 85 and older | 435/1427 (30.5) | 39/171 (22.8) |
| Male sex | 475/1426 (33.3) | 51/172 (29.7) |
| Race |  |  |
| White | 1230/1376 (89.4) | 143/159 (89.9) |
| Black | 111/1376 (8.1) | 11/159 (6.9) |
| Other or more than one race | 35/1376 (2.5) | 5/159 (3.1) |
|  Hispanic | 23/1352 (1.7) | 4/160 (2.5) |
| Enrolled at a Canadian site | 371/1427 (26.0) | 50/172 (29.1) |
| Number of coexisting conditionsa | 1 (0 - 1) | 1 (0 - 1) |
| American Society of Anesthesiologists Physical Status Classification |  |  |
| I or II, no or mild systemic disease | 478/1421 (33.6) | 61/154 (39.6) |
| III or IV, moderate or severe systemic disease | 943/1421 (66.4) | 93/154 (60.4) |
| Do Not Resuscitate status documented | 220/1427 (15.4) | 26/171 (15.2) |
| Use of assistive walking device when ambulating 10 feet or across a room 2 weeks prior to fracture | 450/1402 (32.1) | 47/169 (27.8) |
| 3D-CAM assessment positive for delirium prior to randomizationb | 176/1337 (13.2) | 24/161 (14.9) |
| Pre-admission residence |  |  |
| Home or retirement home | 1228/1349 (91.0) | 149/161 (92.5) |
| Nursing home or other location | 121/1349 (9.0) | 12/161 (7.5) |

Data are No. / total No. (%) or median (IQR).

aIncluded coexisting conditions are chronic pulmonary disease, disseminated cancer, diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, dementia, and creatinine > 2mg/dL or current dialysis. b3D-CAM: 3-minute Diagnostic Interview for

 Confusion Assessment Method.

# Appendix Table 6. Comparison of trial participant characteristics with- and without- missing vital status data at 365 days after randomization

10