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CHARACTERISTICS OF THE DISEASE -- Etiology-Why Do Studies Restrict Inclusion to Aneurysmal Subarachnoid Hemorrhage? -- Pathophysiology Considerations Relevant to Clinical Trials -- Clinical Features and Diagnosis -- GUIDELINES FOR MANAGEMENT OF SUBARACHNOID HEMORRHAGE -- SUCCESSES AND DISAPPOINTMENTS -- Ineffective Interventions -- Treatment Side Effects -- Sample Size and Outcome Measures -- The Quagmire of Rescue Therapy -- Center Variation and Practice Misalignment -- Multifactorial Nature of Delayed Cerebral Ischemia and Prognostic Factors for Outcome -- SUBPOPULATIONS AND OUTCOMES AND THEIR ASSESSMENT. BIOMARKERS AND SURROGATE ENDPOINTS -- PHARMACOKINETICS AND PHARMACODYNAMICS -- CONSENSUS REGARDING FAILURES AND POSSIBLE SOLUTIONS -- CURRENT "STATE OF PRACTICE" IN DESIGN AND ANALYSIS OF RANDOMIZED CONTROLLED TRIALS FOR SUBARACHNOID HEMORRHAGE -- Disclosures -- References -- 3 - Clinical Trials in Spontaneous Intracerebral Hemorrhage -- INTRODUCTION -- HEMATOMA GROWTH -- Blood Pressure -- Hemostasis -- NEUROPROTECTION -- Cerebral Edema -- Neuroinflammation -- Iron Toxicity/Chelation -- Apoptosis -- Cryoprotection -- SURGERY -- CONCLUSIONS -- References -- 4 - Imaging Biomarkers in Stroke Trials -- INTRODUCTION AND DESCRIPTION OF IMAGING BIOMARKERS -- IMAGING OF INTRALUMINAL THROMBUS -- VASCULAR IMAGING -- COLLATERAL ARTERIAL SUPPLY -- ISCHEMIC CORE AND PENUMBRA -- PREDICTIVE VERSUS PROGNOSTIC BIOMARKERS -- UTILITY OF IMAGING BIOMARKERS -- CONCLUSIONS AND FUTURE DIRECTIONS -- References -- II - TRAUMATIC BRAIN INJURY -- 5 - Traumatic Brain Injury -- INTRODUCTION -- HISTORICAL CONTEXT OF TRAUMATIC BRAIN INJURY TRIALS -- DRUG DEVELOPMENT PROGRAMS FOR TRAUMATIC BRAIN INJURY -- Underlying Logic of Traumatic Brain Injury Trials -- Classes of Novel Drugs Tested in Traumatic Brain Injury -- DRUGS AND TREATMENTS TESTED TO DATE FOR TRAUMATIC BRAIN INJURY -- Barbiturates -- High-Dose Corticosteroids -- Tromethamine (THAM) -- ION CHANNEL BLOCKERS -- Free Radical Scavengers -- Glutamate Antagonists -- Glutamate Agonists -- CDP-Choline -- Immune System Modulators -- Statins -- Progesterone -- Hypothermia -- WHY HAVE TRAUMATIC BRAIN INJURY TRIALS PROVEN TO BE SO DIFFICULT? -- KEY ISSUES IN TRAUMATIC BRAIN INJURY CLINICAL TRIAL DESIGN -- Multiplicity of Injuries -- Anatomic Classification of Traumatic Brain Injury -- Treatment-Related Problems -- Limitations of Traumatic Brain Injury Classification -- Limitations of the Outcome Measures -- Glasgow Coma Scale. CT Classification of Traumatic Brain Injury Population -- Prognostic Factors -- Glasgow Outcome Scale -- Outcomes in Traumatic Brain Injury Clinical Trials -- Time Course of Recovery -- Respecifying the Glasgow Outcome Scale -- Shape of Outcome Distribution -- Pharmacokinetic-Pharmacodynamic Correlations -- Censoring Treatment Populations -- CONCLUSIONS -- References -- 6 - Improving Approaches to Evaluate Efficacy and Safety of Drugs for Traumatic Brain Injury -- TRANSLATIONAL APPROACHES -- Extended Experimental Studies -- Better Characterization of Disease Biology and Drug Distribution in Human Traumatic Brain Injury -- IMPROVING TRIAL DESIGN AND ANALYSIS -- Heterogeneity and Statistical Power -- Heterogeneity and Risk of Imbalances -- Dealing With Heterogeneity in Efficacy Analysis -- ALTERNATIVE STRATEGIES TO EXPLORING CLINICAL EFFICACY -- References -- 7 - Brain Imaging in Traumatic Brain Injury -- INTRODUCTION -- TYPES OF BRAIN INJURIES -- Primary Injuries -- Secondary Injuries -- CLASSIFICATION OF TRAUMATIC BRAIN INJURY --

Imaging Modalities -- Conventional Radiography -- Ultrasound -- Computed Tomography -- Computed Tomography Angiography -- Conventional Magnetic Resonance Imaging -- Advanced Techniques -- Diffusion Weighted Imaging-Diffusion Tensor Imaging -- Functional Magnetic Resonance Imaging -- Perfusion Imaging -- Magnetic Resonance Spectroscopy -- Magnetization Transfer Imaging -- Magnetoencephalography -- Single-Photon Emission Computed Tomography -- Positron Emission Tomography -- IMPLICATIONS AND CHALLENGES FOR CLINICAL TRIALS -- CONCLUSION -- References -- 8 - The Use of Blood-Based Biomarkers to Improve the Design of Clinical Trials of Traumatic Brain Injury -- INTRODUCTION -- Traumatic Brain Injury Diagnostics -- Traumatic Brain Injury Management. Recent Successes and Disappointments of Clinical Trials for Novel Drugs to Treat Traumatic Brain Injury Management -- Promises of Biomarker Applications in Traumatic Brain Injury Clinical Trials -- SUMMARY OF SEARCH OF CLINICAL TRIALS IN TRAUMATIC BRAIN INJURY USING BIOMARKERS -- SURROGATE ENDPOINTS AND SELECTION OF CENTRAL NERVOUS SYSTEM-SPECIFIC PROTEIN BIOMARKERS FOR SEVERE TRAUMATIC BRAIN INJURY DIAGNO... -- Biomarkers Potentially Useful in Traumatic Brain Injury Trials -- Biomarkers of Glial Injury -- Glial Fibrillary Acidic Protein -- S100 Calcium Binding Protein B (S100B) -- Biomarkers of Neuronal Injury -- Ubiquitin Carboxy-Terminal Hydrolase L1 -- II-Spectrin Breakdown Products 120, 145, and 150 (SBDP120, SBDP145, SBDP150) -- Microtubule-Associated Protein 2 -- Myelin Basic Protein and Its Autoantibody -- Neuron-Specific Enolase -- Neurofilaments -- Total Tau and Its Cleaved Forms -- Biomarkers of Inflammation and Vascular Injury -- Cytokines -- Cell Adhesion Molecules -- Other Biomarkers -- MicroRNAs -- DISCUSSION -- Improving of the Study Design Using Blood-Based Biomarkers and Their Combination With Other Outcomes Measures -- Statistical Considerations in Clinical Trials Using Biomarker Studies -- PROSPECTS AND PATHWAYS FOR INCORPORATION OF BLOOD-BASED BIOMARKERS INTO THE DESIGN OF CLINICAL TRIALS FOR TRAUMATIC BRAIN INJURY... -- References -- 9 - Biostatistical Issues in TBI Clinical Trials -- INTRODUCTION -- CLINICAL TRIAL DESIGN -- Dose-Finding Designs -- Selection Designs -- Futility Designs -- Confirmatory Designs -- Adaptive Designs -- APPROACHES TO RANDOMIZATION -- Achieving Balance With Respect to Known Prognostic Variables -- Covariate-Adaptive Randomization -- Response-Adaptive Randomization -- Comparing Baseline Characteristics in a Randomized Trial -- OUTCOME MEASURES -- Glasgow Outcome Scale/Glasgow Outcome Scale Extended. Performance-Based Measures -- Patient-Reported Outcomes -- Clinician-Reported Outcomes -- Biomarkers -- ANALYTICAL APPROACHES -- The Fixed Dichotomy -- The Sliding Dichotomy -- Ordinal Analysis -- MISSING DATA -- MULTIPLICITY -- SUBGROUP ANALYSIS -- ASSESSMENTS CONDUCTED OVER TIME -- HETEROGENEITY OF THE PATIENT POPULATION -- SUMMARY -- References -- III - SEIZURE EMERGENCIES -- 10 - Acute Seizures and Status Epilepticus -- OVERVIEW -- DIAGNOSIS AND DEFINITION OF STATUS EPILEPTICUS -- CLASSIFICATION OF STATUS EPILEPTICUS -- Semiology -- Etiology -- Electroencephalographic Correlates -- Age -- ANIMAL MODELS: RELEVANT ISSUES FOR CLINICAL DEVELOPMENT PROGRAMS -- EPIDEMIOLOGY AND NATURAL HISTORY -- Acute Repetitive Seizures -- Generalized Convulsive Status Epilepticus -- Refractory Status Epilepticus -- Super-refractory Status Epilepticus -- Nonconvulsive Status Epilepticus -- MECHANISMS OF DISEASE AND PATHOLOGY -- DIAGNOSIS AND SUBPOPULATIONS -- Severity of Injury

Measures -- Seizure Type -- Level of Consciousness -- Duration -- Response to Treatment (Status Epilepticus Stage) -- Etiology -- Concomitant Medical Illnesses -- Defining Relevant Treatment Populations -- Defining Good and Poor Prognoses -- Relevant Prognostic Factors for Defining Inclusion and Exclusion Criteria -- Subsetting Patients for Planned and Ad Hoc Comparisons -- CURRENT DISEASE MANAGEMENT AND CONTROVERSIES -- Initial Management Steps -- Prevention of Status Epilepticus: Acute Repetitive Seizures -- Generalized Convulsive Status Epilepticus -- Early Status Epilepticus Treatment -- Established Status Epilepticus -- Refractory Status Epilepticus and Super-refractory Status Epilepticus -- Nonconvulsive Status Epilepticus -- Specific Drugs -- ISSUES IN CLINICAL PROTOCOL DEVELOPMENT -- Time to Treatment -- Operational Definitions of Status Epilepticus -- Site Selection -- Sample Size. Treatment Selection.

Sommario/riassunto

Handbook of Neuroemergency Clinical Trials, Second Edition, focuses on the practice of clinical trials in acute neuroscience populations, or what have been called neuroemergencies. Neuroemergencies are complex, life-threatening diseases and disorders, often with devastating consequences, including death or disability. The overall costs are staggering in terms of annual incidence and costs associated with treatment and survival, yet despite their significance as public health issues, there are few drugs and devices available for definitive treatment. The book focuses on novel therapies and the unique challenges their intended targets pose for the design and analysis of clinical trials. This volume provides neurologists, neuroscientists, and drug developers with a more complete understanding of the scientific and medical issues of relevance in designing and initiating clinical development plans for novel drugs intended for acute neuroscience populations. The editors provide the best understanding of the pitfalls associated with acute CNS drug development and the best information on how to approach and solve issues that have plagued drug development. Presents a comprehensive overview on clinical trials and drug development challenges in acute neuroscience populations Provides neurologists, neuroscientists and drug developers with a complete understanding of scientific and medical issues related to designing clinical trials Edited by leaders in the field who have designed and managed over 50 neuroemergency clinical trials