BioTrak RESEARCH

CAPABILITIES AND METHODOLOGY REVIEW FOR REMS ASSESSMENTS

March 1, 2011 • CONFIDENTIAL

About BioTrak

- **Founded in 1999 to provide commercial support and new product planning consulting services to the pharmaceutical and medical device industry**
- **Team of researchers, pharmacists, regulatory, biostatistics experts, and support staff based in Carlsbad, California**
- **Conducted over 285 total research studies and over 60 web-based questionnaire survey studies with patients, health care providers, and pharmacists**
- **Recent and relevant REMS and pharmaceutical risk management consulting experience**
- **Considered a leader and innovator in REMS assessments**
- **Proprietary and novel analytical toolbox for assessments**
- ***Business entirely focused on REMS solutions and observational research***

Industry Best Practices in REMS Assessments

- **Design of successful REMS assessment protocols with expertise in:**
  - Protocol design
  - Sampling strategy
  - Questionnaire development and secure internet survey hosting (since 2002)
  - Survey pretesting validation processes including literacy review options
  - Multimodal recruitment approaches
  - Statistical analysis and reporting metrics
- **Proprietary web survey portal providing easy but well controlled online survey access at www.treatmentsurvey.com**
- **Real-time assessment reporting through "PharmaTrak Viewer"**
- **Clinmetric™ ASSESS, the first of its kind analytical tool and database which helps with selection of appropriate REMS assessment performance metrics, interpretation of results, and determination of corrective actions.**
- **Bilingual, HIPAA compliant call support**
- **Comprehensive regulatory compliance and quality assurance program**

REMS Assessment Consulting Experience

Examples of Risk Evaluation and Mitigation Strategy (REMS) Experience				
Disease Area	**Sample**	**Product**	**Type of Research Study**	**Methodology**
Antiviral	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Antiviral	Patients	Existing Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Antiviral	Patients	Existing Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Antiviral/Oncology	Patients	Existing Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Asthma	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Cardiovascular	Patients and Prescribers	New Rx Medication	**REMS Assessment** for measuring]understanding of medication risks, appropriate use, and medication guide distribution compliance	Web-Based and Call Supported Survey
Cardiovascular	Patients	Existing Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
CNS	Patients and Physicians	New Rx Medication	**REMS Assessment** for measuring]understanding of medication risks, appropriate use, and medication guide distribution compliance	Web-Based and Call Supported Survey
CNS	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
CNS	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
Diabetes	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
Diabetes	Patients	Existing Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
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Epilepsy	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
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REMS Assessment Consulting Experience

Examples of Risk Evaluation and Mitigation Strategy (REMS) Experience				
Gastroenterology	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
Gastroenterology	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
Metabolic	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Oncology	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Pain	Patients	New Rx Medication	**REMS Assessment** for measuring understanding of the serious medication risks	Web-Based and Call Supported Survey
Pain	Patients and Physicians	New Rx Medication	**REMS Assessment** for measuring understanding of serious risks and medication guide distribution compliance	Web-Based and Call Supported Survey
Surgical/Other	Patients and Physicians	New Rx Medication	**REMS Assessment** for measuring]understanding of medication risks, appropriate use, and medication guide distribution compliance	Web-Based and Call Supported Survey
Transplantation	Patients and Prescribers	New Rx Medication	**REMS Assessment** for measuring]understanding of medication risks, appropriate use, and medication guide distribution compliance	Web-Based and Call Supported Survey
Transplantation	Patients and Prescribers	Existing Rx Medications	**Elements to Assure Safe Use Program, Shared REMS. REMS assessment** design and implementation for patients and health care providers to measure REMS performance	Web-Based and Call Supported Survey

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REMS Assessment Clients

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Methodology for a "DRUG A" REMS Assessment Program

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DRUG A REMS Assessment Objectives

1) **Measure Patients' understanding of the serious risks of DRUG A.**

2) **Report on the distribution and dispensing of the medication guide in accordance with 21CFR208.24 (if not a unit of use).**

3) **Reporting on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance (if not a unit of use).**

The results of this assessment will inform the Sponsor and the FDA if the DRUG A REMS program is effective in achieving its goals and if REMS modification or corrective actions are warranted.

DRUG A REMS Assessment

Proposed study methodology is based upon

- Extensive experience with REMS and REMS assessments
- Current FDA “guidance”

Utilizes customized analysis tools

- PharmaTrak™ Viewer
- Clinmetric™ ASSESS

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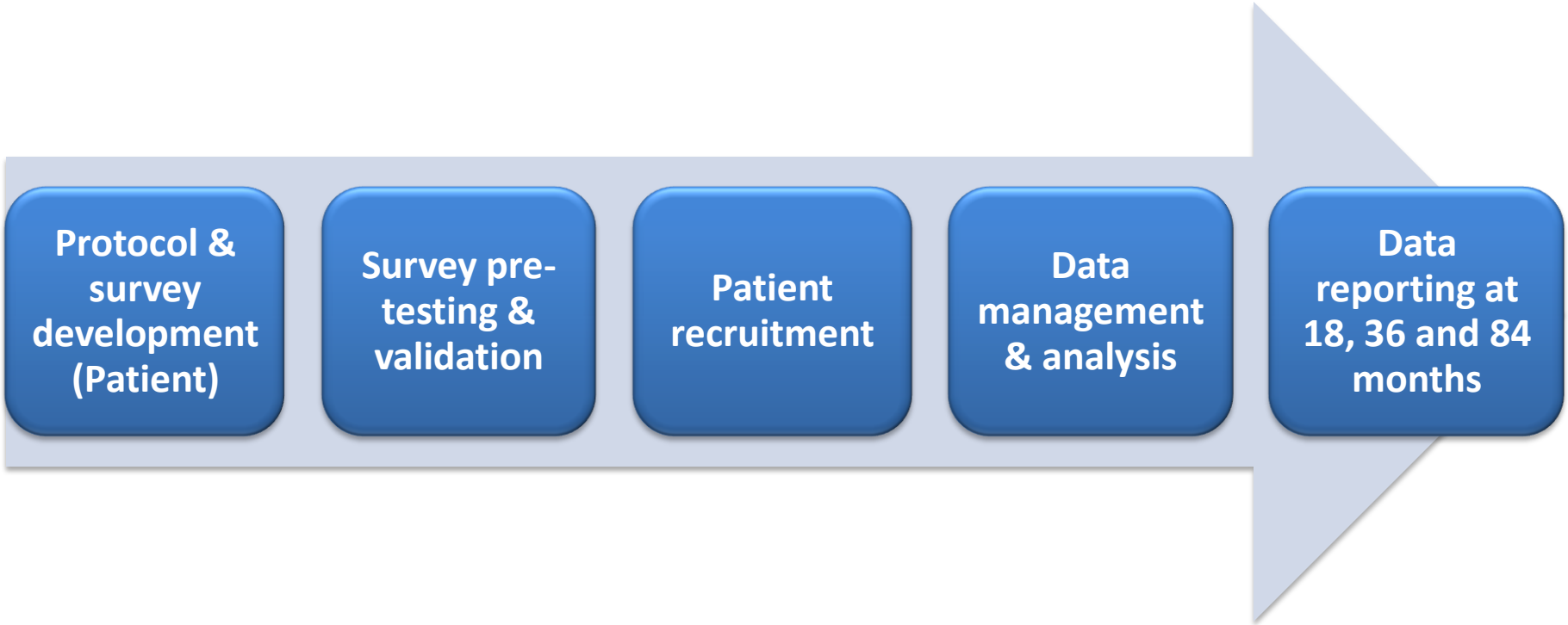
DRUG A REMS Assessment

Internet-hosted survey tool with call-supported option



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DRUG A REMS Assessment

- **DRUG A REMS Assessment protocol will include descriptions of**
  - **Proposed evaluation method**
  - **Sample size and associated confidence interval**
  - **How the sample will be determined (selection criteria)**
  - **Expected number of patients to be surveyed**
  - **How and how often the patient surveys will be administered**
  - **Controls used to minimize bias**
  - **Survey instruments**
  - **Background information for testing survey questions**
  - **Analyses to be used to assess performance**

DRUG A REMS Assessment

1. **"Consent to Participate in Survey"**
   - Study purpose
   - Participant fee
   - Confidentiality

2. **Eligibility questions**
   - Age
   - Prescription filled
   - Prescription fill date

3. **Multiple choice questions (10-15) limited to serious risks that include:**
   - True/false
   - "Select all that apply" or "None of the above"
   - "I don't know" or "I don't recall"

Based upon FDA Preferences

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Survey Pretesting & Validation

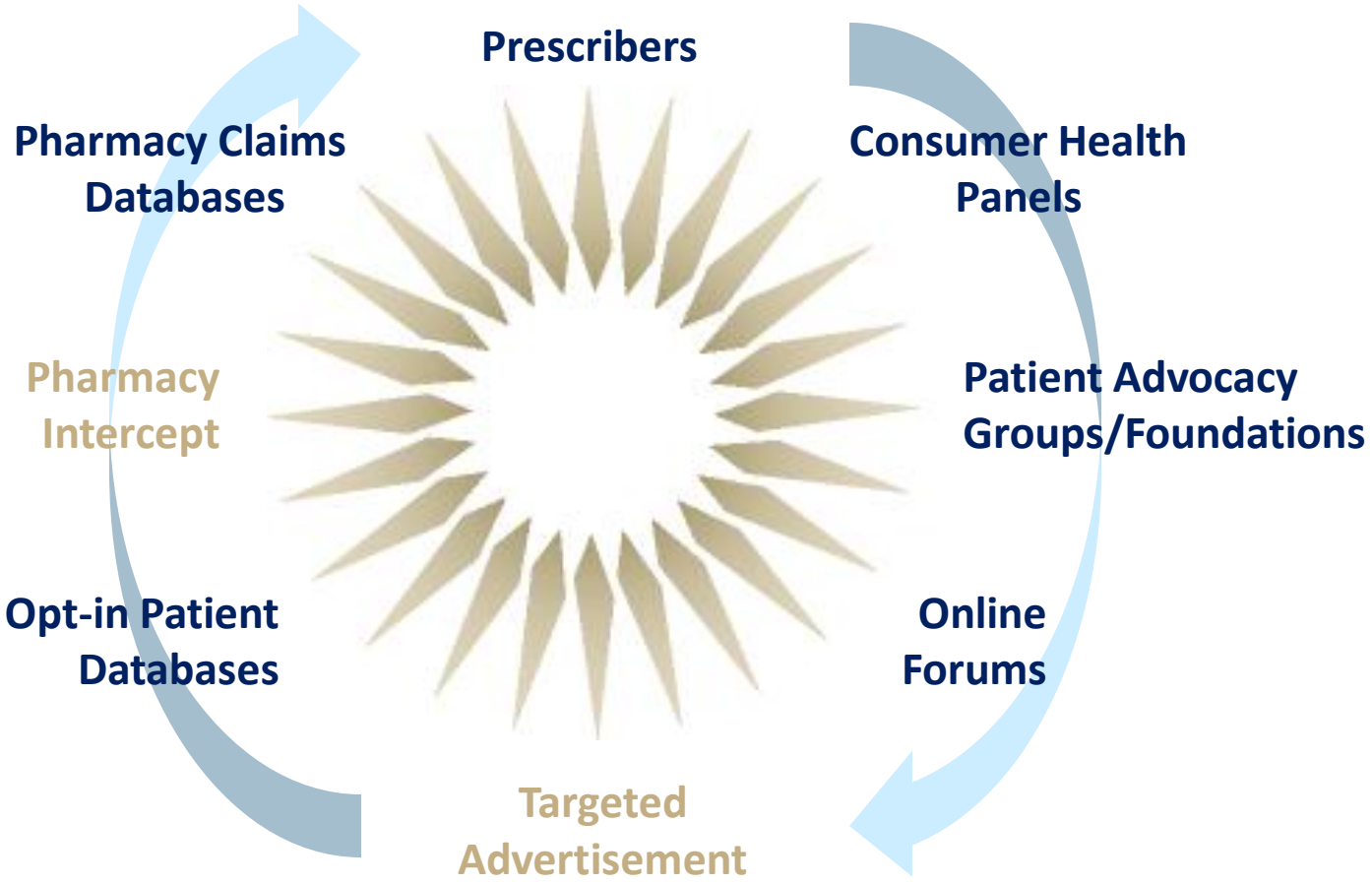
- **Recommendation to pretest the surveys with a cohort of 15 patients to determine readability and understanding of the proposed survey questions.**
  - Respondents given MedGuide to review and survey to complete
  - Respondents asked follow-up questions to evaluate clarity and comprehension of each question

- **Data integrity testing performed with all possible choices using predesigned response grid to ensure accurate programming functionality and data capture.**

- **Pretesting and validation study report provided to Sponsor.**

Findings and recommendations for any language or question revisions to the survey are reported

Multimodal Recruitment Method Meets the FDA's Sampling Expectations



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FDA Recommended Sample Size

- **Sample size recommendation (per reporting period)**
  - 200 patients; yields a 6% Confidence Interval at a 60% rate

Binomial Test 95% Exact One-Sided Confidence Interval

N	Nominal Rate	True Rate	Lower Exact 95% Boundary	Lower Boundary Drop from True Rate
150	0.6	0.6	0.52981	0.07019
200	0.6	0.6	0.53968	0.06032
250	0.6	0.6	0.54634	0.05366
300	0.6	0.6	0.55122	0.04878

- **Based upon:**
  - FDA input on measuring patients understanding of serious drug risk (at least 200 or 250 preferred)
  - Quantitative drug analyses using a 95% CI to inform reporting domains
  - Knowledge, awareness, and understanding of serious risks, dispensing rates and distribution reach of the MedGuide.

Predicting Achievable Sample Size

Guidelines to Predict Achievable Sample			
Scenario	Confident	Possible	Highly Uncertain
Reachable patient population*	30%	40%	50%
Survey invitation response rate	15%	20%	30%
Expected survey incidence rate of treated population	4.5%	8%	15%

**Assumes Sponsor has complete patient list*

FDA Preferred Sample Sizes

- **In the case of an insufficient DRUG A prescriber base and patient population during a reporting period:**
  - A smaller sample size may be warranted for that assessment report.
  - The survey can run continuously and, in addition to the required reporting dates, a voluntary analysis can later be reported to the FDA when the appropriate sample size is achieved.
- **Most sample shortfalls are a result of the Sponsor initiating the REMS assessment effort too late in the reporting period.**

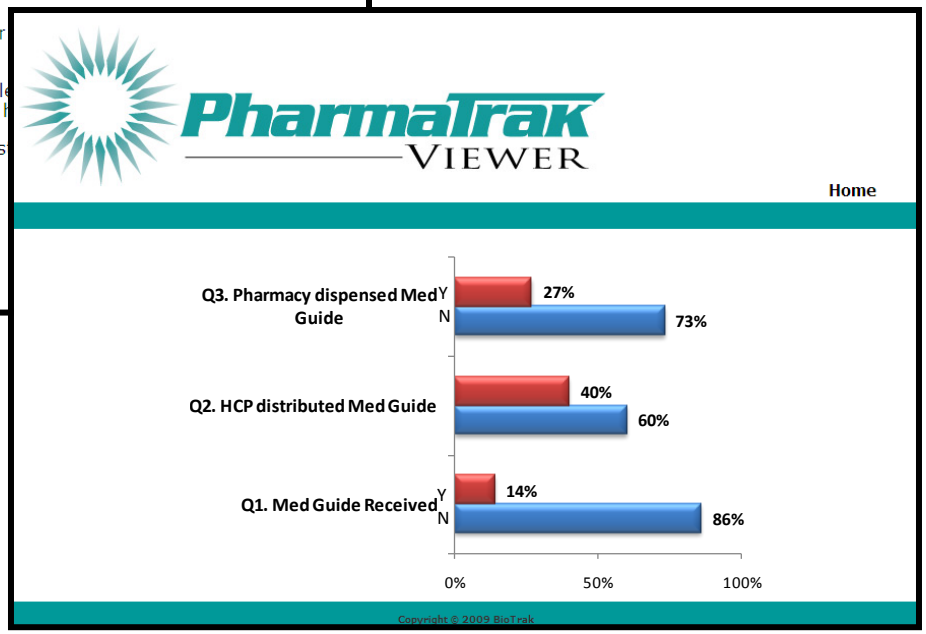
FDA Preferred Sample Sizes

- **2009 FDA Draft Guidance REMS regarding reporting intervals**
  "…the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment."

- **Sponsor may view ongoing results through a client-specific web portal or request results at any ad-hoc interval period**

  - Centralized assessment portal for easy stakeholder and client access
  - Unique client specific dashboard for real-time assessment reporting

Real-Time Assessment Results



Centralized assessment portal for easy stakeholder and client access

Unique client specific dashboard for real-time assessment reporting

Proprietary web coding and database system verifies survey code authorization, and directs to appropriate survey

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Reporting Methodology

- **Assessment results will be analyzed:**
  - In aggregate
  - By reporting domain
  - By serious risk message
  - On a question item-by-item basis
- **Data will be reported using inferential and simple descriptive statistics**
- **Clinmetric™ ASSESS tool and database**
  - Tool can generate appropriate performance benchmarks. Provides greater interpretation of the DRUG A REMS assessment results and the need for corrective actions, if any.

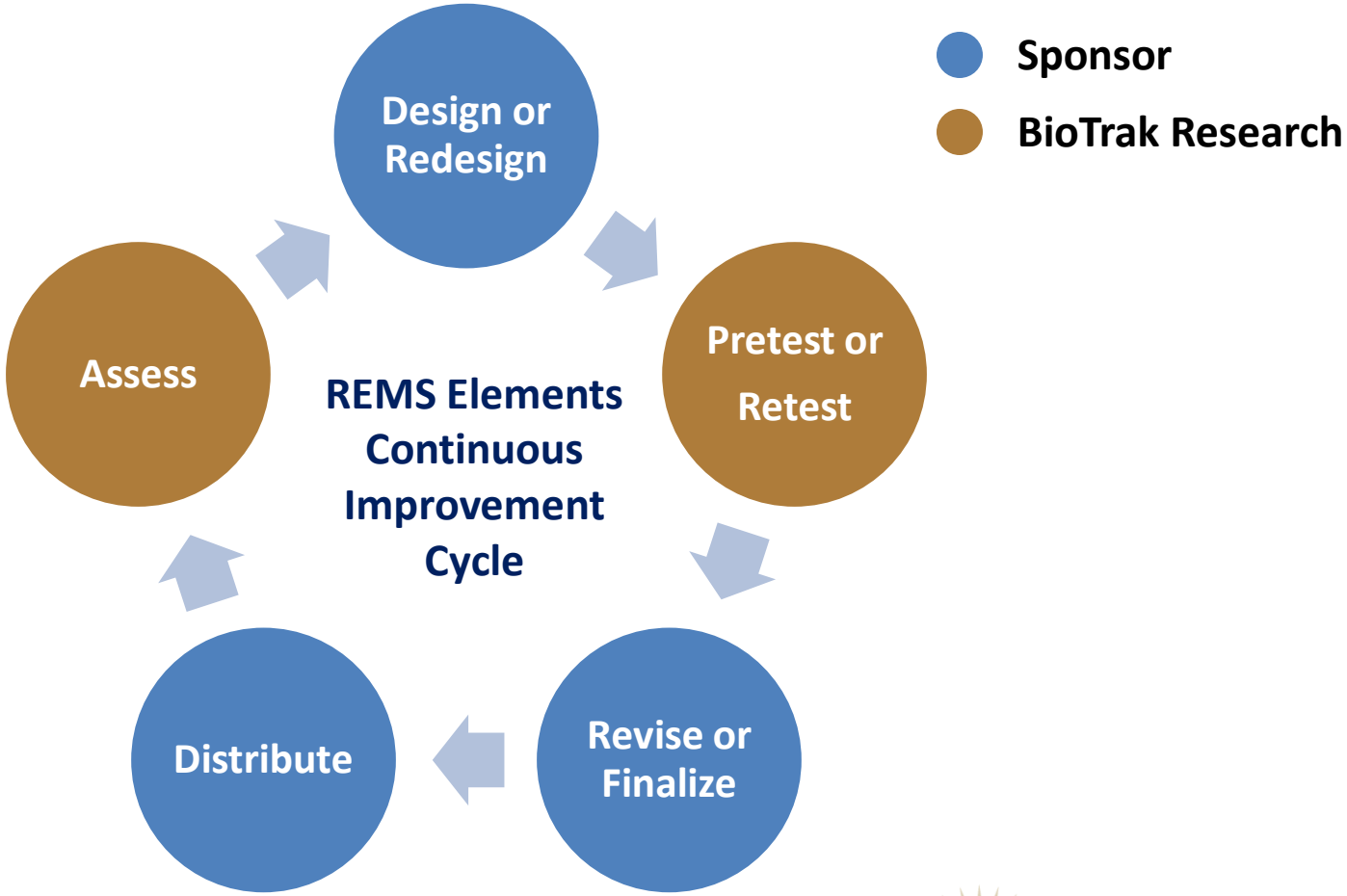
Expected Results

- **Patients understanding of the serious risks**
  - Performance determined by multiple factors, e.g.,
    - Receipt of MedGuide and how it is presented (separate or part of the PI)
    - Number of serious risk messages
    - Severity of illness
    - Role of caregiver, age of survey taker
    - Rate of HCP and pharmacy counseling

- **Most REMS assessments are identifying shortcomings with the effectiveness of MedGuides, putting Sponsors in a position to revise them for improved risk communication.**

- **Clinmetric™ ASSESS may be utilized in this multi-factorial analysis to establish appropriate performance benchmarks for DRUG A and to determine what, if any, corrective actions must be taken.**

EFFECTIVE RISK COMMUNICATIONS



THE FDA HAS AUDITED SPONSORS AND VENDORS ON REMS!

BioTrak Research offers industry best practices in compliance:

- ✓ **Good Clinical Practice (GCP) and Good Documentation Practice (GDP) compliance procedures and training program. Complete SOP system covering all facets of REMS assessments (30+ SOPs).**
- ✓ **Privacy and Security compliance procedures and training program and designated Officer**
  - **100% of staff NIH certified in human subjects research and privacy**
- ✓ **Data management safeguards**
  - **Secure server - Physical and IP security measures (i.e., intrusion detection, encryption security, locked restricted access room)**
  - **Remote (offsite) backup and disaster recovery plan**
  - **Offer SSH that is user name/password authenticated**
  - **SSL on all data collecting websites**
- ✓ **Ethics policy, training, and designated Ethics Officer**
- ✓ **In compliance with all federal, state and local laws – no history of non-compliance**

3 Reasons to Choose BioTrak Research

Extensive REMS Assessment Expertise

- Since the implementation of REMS in March 2008, BioTrak Research has lead REMS assessment, design, implementation, and reporting for **31 assessments** covering **27 products.**

Proprietary Analysis Tools and Reporting Know How

- Our proprietary analytical tools and methods such **as Clinmetric™ ASSESS** and **PharmaTrak Viewer**, combined with experience reporting on REMS, brings new meaning to REMS assessments. These capabilities enhance results interpretation and provide early signal detection leading to improved risk mitigation and acceptance by the FDA.

REMS Regulatory Compliance and Industry Best Practices

- We have a **complete GCP and GDP program** built for REMS assessments that meets and exceeds current regulatory compliance requirements. Our methods align with FDA expectations and can be considered industry's best.

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Key Management Team

Larry A. Risen, President

- 25 years medical industry commercial experience
- Project leader/director on over 285 consulting assignments involving drug safety, human factors research, labeling comprehension, product planning, commercial strategy, and commercial support services. This included 27 REMS assignments, over 60 web-hosted patient and prescriber surveys, and a broad range of commercial research.
- Managed 20 new product launches – 3 Rx, 17 Dx
- Built 2 specialty pharma commercial programs from ground up
- Designed novel, reliable and predicable methods for REMS assessments

Mr. Risen founded BioTrak in 1999. Prior to BioTrak, Mr. Risen was Vice President of Commercial Development at Cypros Pharmaceutical Corporation (now Questcor) from 1994 to 1999, where he built a sales and marketing organization, coordinated development of a new drug distribution facility, and completed several product licensing deals. Prior to Cypros, Mr. Risen held various management level positions in marketing and product development while at Gen-Probe Inc. and Molecular Biosystems Inc. Mr. Risen received his Bachelor of Science degree in Biology from the University of Iowa and completed his MBA studies at the University of San Diego. He has been a featured speaker at national and regional industry conferences and has authored several articles and videos on REMS assessment, REMS program design, and labeling comprehension studies.

Karl Cremer, PharmD, Vice President

- 25 years clinical development experience from IND/IDE to NDA/PMA
- Clinical liason and safety officer for REMS assessment programs
- Study director for over 50 Phase I to Phase III clinical studies leading to multiple approvals
- Project manager for 4 clinical development programs into Phase III
- Experienced with both remote and web-based EDC systems
- Currently BioTrak's PharmaTrak™ Vice President and Senior Consultant

Dr. Cremer has 25 years of academic and industry clinical research and regulatory experience in a wide variety of therapeutic areas including oncology, cardiology, pulmonary, neurology, hematology, and infectious diseases. For the last seven years, he has provided clinical research, regulatory and business development consulting services to emerging pharmaceutical and medical device companies. He has held management positions at four medical device and pharmaceutical companies (IVAC, Gensia, Alliance, and Cypros) where he managed domestic and international clinical trials resulting in one drug and two medical device approvals. Prior to his roles in industry, Dr. Kramer was an Assistant Professor at the University of Texas Health Science Center in San Antonio where he taught clinical pharmacy and pharmacokinetics.

Key Management Team

Gerard Smits PhD, Senior Consultant
Biostatistics and Data Management

Dr. Smits brings over twenty years of biostatistical experience with pharmaceutical, device, and biotech companies, working for 19 years as an independent consultant. He provided statistical support on pre-clinical through phase IV studies on a wide variety of indications (e.g., oncology, renal disease, anemia, heart failure, myocardial infarction, hepatitis B and C, hypertension, insomnia, vision correction, robotic surgical intervention, surgical treatment of obesity, and CNS trauma). His responsibilities have ranged from study design and formulation through statistical analysis, table production, writing of statistical reports, meetings with the FDA as needed, including panel meetings, and have served as a DSMB member. Dr. Smits has managed clinical trials, survey research, and human factors projects. Taught several courses SAS, having 28 years experience with the statistical package. Dr. Smits is proficient with StatXact (exact statistical tests), and PEST (group sequential methods), and R (a general data analysis program) and able to explain complex statistical concepts in terms understandable to non-statisticians.

Contact

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