Innovative Clinical Development Solutions

From Protocol to Package Insert:
A Data Journey

AMWA Medical Writing & Communication Conference

Thursday, November 1, 2018

PROMETRIKA
A FULL-SERVICE CRO

Introductions

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Senior Manager,
Medical Writing

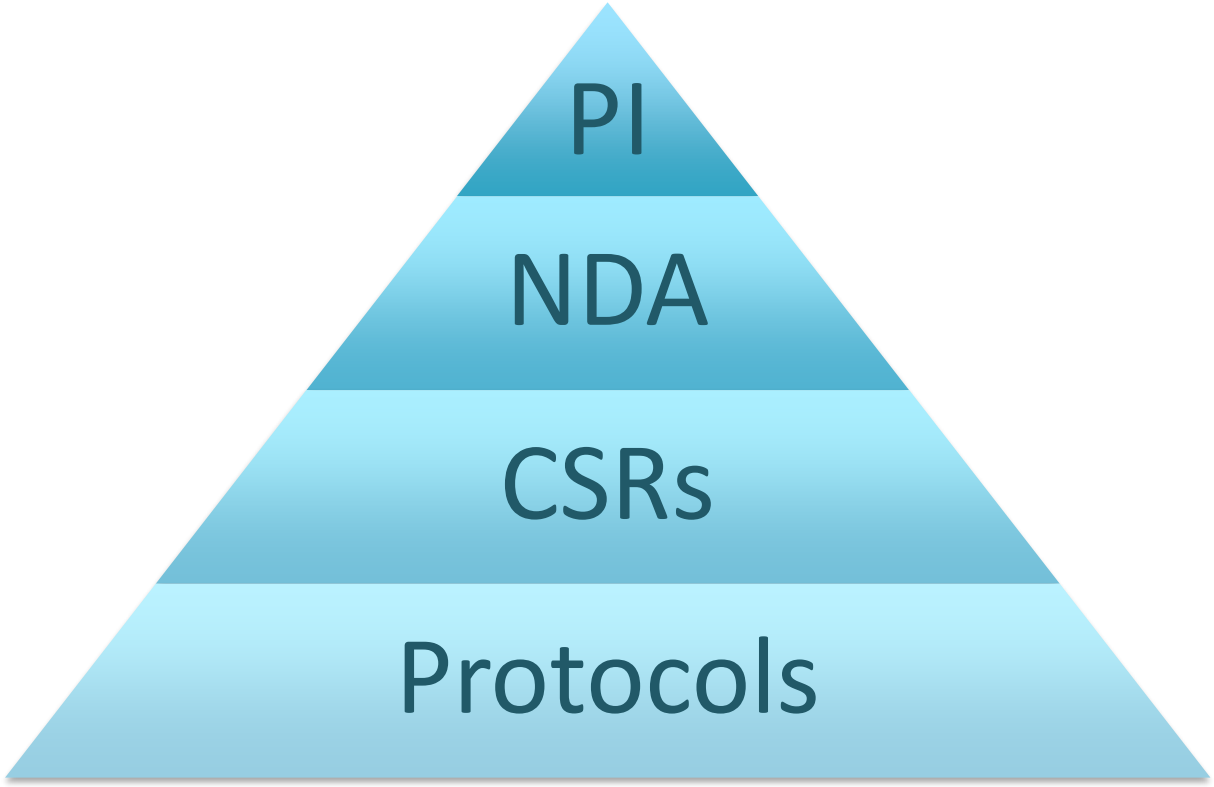
- 30+ years biopharmaceutical industry; 25+ as a regulatory writer
- Career: 12 NDAs (ISS/E, Clinical Summaries)
- BA Biology, MT(ASCP) (no longer active)

Christine Quagan

Senior Medical Writer

- 20+ years biopharmaceutical industry; 15+ as a regulatory writer
- Career: 5 NDAs, briefing document, DSURs, many CSRs
- BA Biochemistry; Technical Communications Certificate; AMWA Core Curriculum Certificate (2010)

Derivation of Package Insert



The Industry in Acronyms

What does PI stand for?

- Principal Investigator
- Personal Information
- Patient Information
- Package Insert
- Product Information
- Prescribing/Prescriber's Information

How about "label?"

- Depends on context
- PI (see left)
- Physical label on product and packaging

The Writer & the Clinical Program

Ideal	Reality
“Write the label first”	Set goals for clinical program

The writer’s role:
Familiarity with the goals & messages

Physician Labeling Rule (PLR)

- Final Rule: 21 CFR parts 201, 314, and 601
- PLR format: 21 CFR 201.56 and 201.57 (Jan 2006)
  - Highlights
  - Table of Contents
  - Full Prescribing Information (FPI)
- Objective of PLR Format: provide the Health Care Professional (HCP) with an adequate summary for making treatment decisions

PLR Highlights Section

NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

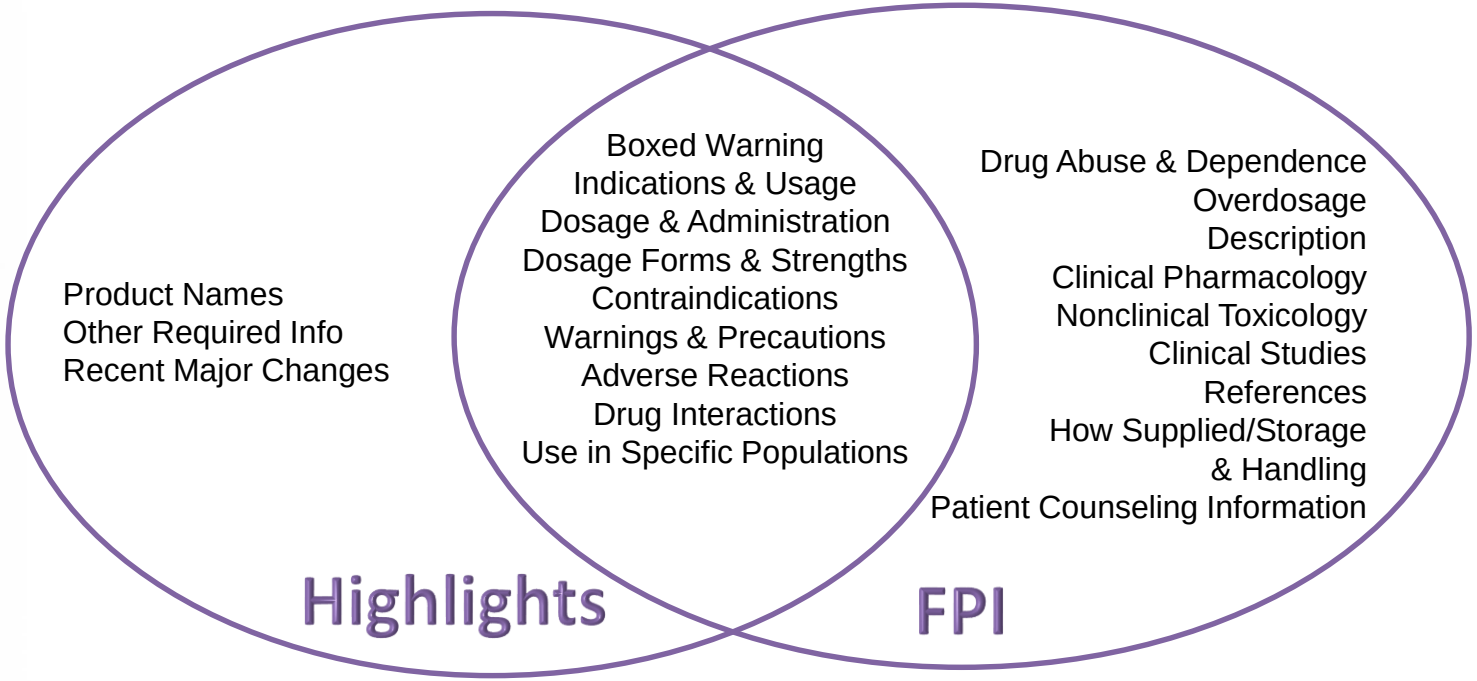
----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

PLR Format



Guidance: Labeling for Human Prescription Drug and Biologic Products – Implementing the PLR Content and Format Requirements. Feb 2013
Draft Guidance: Indications and Usage Section of Labeling for Human Prescription Drug and Biologic Products – Content and Format. July 2018

Indications & Usage

- Newest draft guidance, July 2018
- Enables HCPs to identify therapies by clearly communicating the drug's approved indication(s)

Indication & Limitations of Use

- Must state that the drug is indicated for the treatment, prevention, mitigation, cure, diagnosis, manifestation, or relief of symptoms of a recognized disease or condition
- Scope of the population(s) for which the drug is approved, including age groups
- Include relevant qualifiers to the population, adjunctive/concomitant therapy, specific tests needed
- Example: Drug-X is indicated for the treatment of adult and pediatric patients 12 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- Example: Drug-X is indicated in adults for the treatment of high-grade malignant glioma as an adjunct to surgery and radiation.

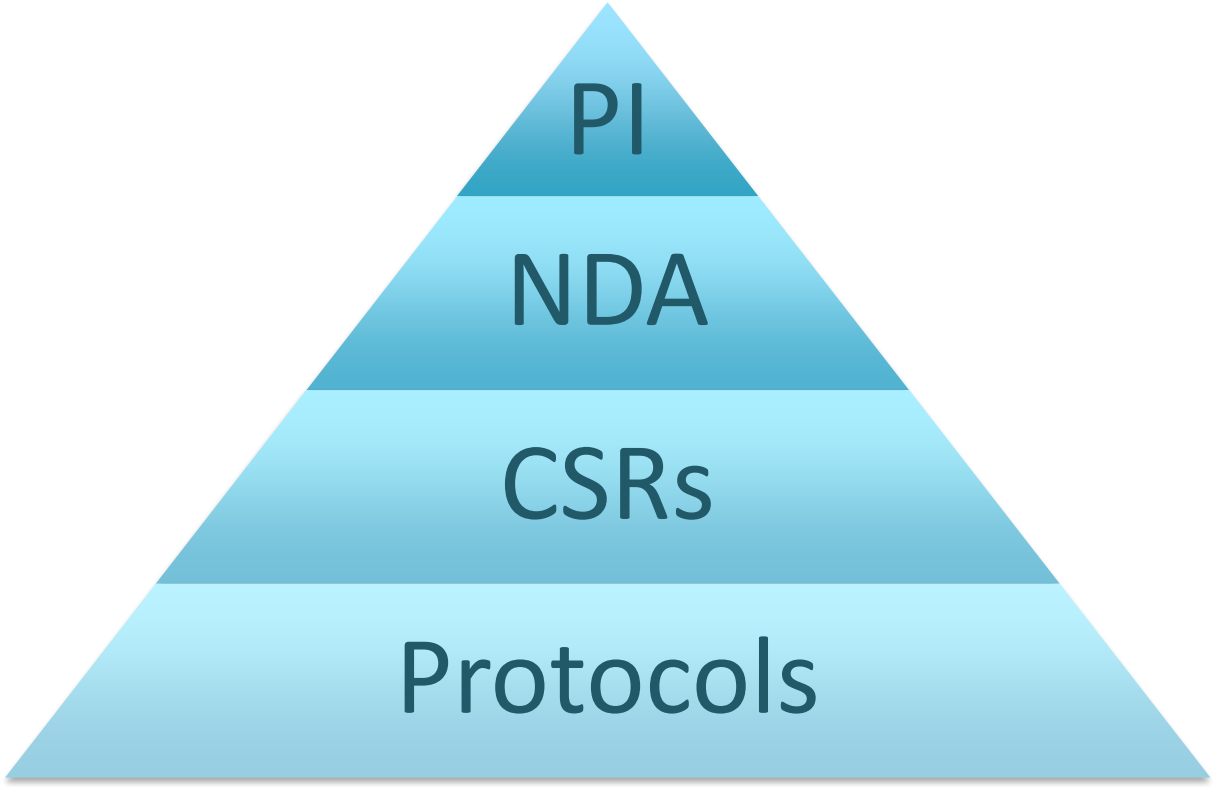
Indications & Usage

- Limitations of Use
  - A “limitation” has less severe consequences than a “contraindication”
  - Contraindication: the drug should not be used because the risk (e.g., potentially fatal adverse reactions) clearly outweighs the possible benefit
  - Limitation: evidence falls short of requiring a contraindication but suggests use may be inadvisable; there is sufficient concern or uncertainty about risks or benefits in certain situations to suggest the drug should not be used in those situations

Example Limitations of Use

- Indication
  - Drug-X is indicated for the treatment of hypertension in adults and pediatric patients 1 year of age or older.
- Limitations of Use
  - In patients younger than 1 year of age, Drug-X can adversely affect kidney development.

Derivation of Package Insert



What is an Adverse Reaction?

- Definition of adverse reaction (AR): an undesirable effect reasonably associated with the use of a drug
- Sponsor's assessment - not all adverse events (AEs)
- Relationship determined by pooling of data across studies, knowledge of effects of drug class, reports in literature, post-marketing reports
- Goal: information that helps HCPs make treatment decisions and monitor and advise patients

Guidance: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, Jan 2006

Contents of the Adverse Reactions Section

Standard disclaimer: limits of applicability of AR rates in clinical trials

- Clinical trial database is the source of AR data
  - Exposure, demographics, trial design
- Clinical trials AEs & post-marketing AEs listed separately
- Serious ARs cross-referenced & discussed in other sections (WARNINGS & PRECAUTIONS, CONTRAINDICATIONS)
- AEs by incidence (eg, ≥10% in the treatment group and at least twice the placebo rate) & with clinical implications (eg, discontinuation, clinical intervention).

Sample Adverse Reactions Section

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

→ Disclaimer

Across two trials, 200 patients with indication were treated with StudyDrug. This included 120 patients treated with StudyDrug and 115 patients treated with placebo in a 16-week, randomized, double-blind study and 80 patients treated with StudyDrug and 75 treated with placebo in a 12-week randomized double-blind study. Dosage regimens in these trials ranged from 200 mg to 600 mg of StudyDrug.

→ Description of Database

Adverse reactions reported in at least 5% of patients treated with StudyDrug in these trials are listed in Table 1.

→ Criteria for Inclusion

Table 1: Adverse Reactions Reported in Two Clinical Trials in at Least 5% of Patients Receiving StudyDrug

Body System Adverse Reaction	StudyDrug % (N=200)	Placebo % (N=190)
Any Adverse Reaction	75	65
Gastrointestinal Disorders		
Diarrhea	24	11
Constipation	20	10
Nausea	11	5
Abdominal Pain	6	3

Table of events sorted by body system & frequency

Sources of Adverse Reactions Section

ISS

System Organ Class Preferred Term, n (%)	SDR-0123 (N=200)	Placebo (N=190)
Any TEAEs	150 (75.0)	124 (65.3)
Gastrointestinal Disorders	81 (40.5)	57 (30.0)
Diarrhoea	48 (24.0)	21 (11.0)
Constipation	40 (20.0)	19 (10.0)
Nausea	22 (11.0)	9 (4.7)
Abdominal pain	12 (6.0)	6 (3.2)

System Organ Class Preferred Term, n (%)	SDR-0123 (N=120)	Placebo (N=115)
Any AEs	95 (79.2)	78 (67.8)
Gastrointestinal Disorders	49 (40.8)	35 (30.4)
Diarrhoea	30 (25.0)	16 (13.9)
Constipation	24 (20.0)	12 (10.4)
Nausea	13 (10.8)	6 (5.2)
Abdominal pain	9 (7.5)	3 (2.6)

Study A

System Organ Class Preferred Term, n (%)	SDR-0123 (N=80)	Placebo (N=75)
Any AEs	55 (68.8)	46 (61.3)
Gastrointestinal disorders	32 (40.0)	22 (29.3)
Diarrhoea	18 (22.5)	5 (6.7)
Constipation	16 (20.0)	7 (9.3)
Nausea	9 (11.3)	3 (4.0)
Vomiting	5 (6.2)	4 (5.3)

Study B

Why Are AEs Collected?

- Identify events that are drug related or potentially drug related
- Increase understanding of drug toxicity & dose-related drug toxicity
- Modify study protocols if necessary to protect subject safety
- Adhere to regulatory requirements designed to protect study subjects, prescribing physicians, & Sponsors

AE Collection Directed by Protocol

Definition: any undesirable event that occurs in conjunction with use of a drug, whether or not drug-related.

- Protocol directs collection of AEs during the study
  - **Timing:** when to collect & how long to follow up
  - **Severity:** mild, moderate, severe, life-threatening, fatal
  - **Relationship to study drug:** definite, probable, possible, unlikely, unrelated
  - **SAE definition(s) & reporting:** Sponsor notified separately; event recorded both in a safety & a clinical database
  - **Laboratory test results:** abnormalities that must be reported as AEs

Contents of the Clinical Studies Section

- Studies that facilitate understanding drug use
  - Summarize evidence of effectiveness in the population studied
- Studies that demonstrate effectiveness in the approved indication
  - Critical study design elements, population(s), endpoints
- Clear terminology
- No implication for unapproved indications or regimens
  - “Off-label”
- How much detail? See Guidance.

Guidance: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, Jan 2006

Sample Clinical Studies Section

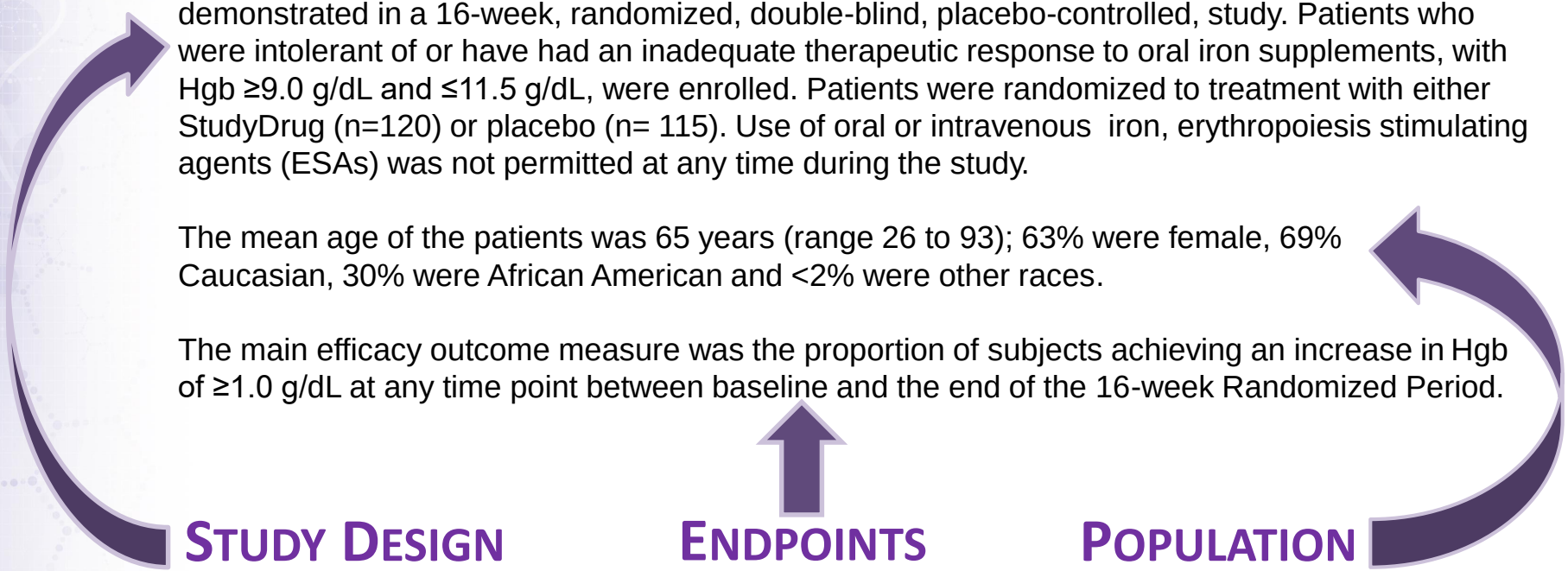
14 CLINICAL STUDIES

14.1 Study DCO-ABC-123

The efficacy of StudyDrug for the treatment of iron deficiency anemia in adult patients was demonstrated in a 16-week, randomized, double-blind, placebo-controlled, study. Patients who were intolerant of or have had an inadequate therapeutic response to oral iron supplements, with Hgb ≥9.0 g/dL and ≤11.5 g/dL, were enrolled. Patients were randomized to treatment with either StudyDrug (n=120) or placebo (n= 115). Use of oral or intravenous iron, erythropoiesis stimulating agents (ESAs) was not permitted at any time during the study.

The mean age of the patients was 65 years (range 26 to 93); 63% were female, 69% Caucasian, 30% were African American and <2% were other races.

The main efficacy outcome measure was the proportion of subjects achieving an increase in Hgb of ≥1.0 g/dL at any time point between baseline and the end of the 16-week Randomized Period.



Sample Clinical Studies Section

Table 4: Efficacy of StudyDrug in Iron Deficiency Anemia

	StudyDrug (N=120)	Placebo (N=115)	p-value
Proportion of patients achieving an increase in hemoglobin of ≥ 1.0 g/dL at any time point during the 16 week study	52%	19%	<0.001

Table 8: Analysis of Proportion of Subjects Achieving an Increase in Hgb of ≥1.0 g/dL From Baseline at Any Study Point Until End of the Randomized Period (ITT Population)

	SDR-0123 (N=120)	Placebo (N=115)	Proportion Difference (95% CI) (SDR-0123 - Placebo)	P-value
Responder	61 (52.1%)	22 (19.1%)	33.0% (21.4%, 44.6%)	<0.001
Non-responder	56 (47.9%)	93 (80.9%)		

Study DCO-ABC-123

How Efficacy Endpoints Are Selected
Considerations & Confounders

- “Current” medical science & treatments
- Findings of the clinical program
- FDA and clinical outcomes considerations

Endpoint Collection Directed by Protocol

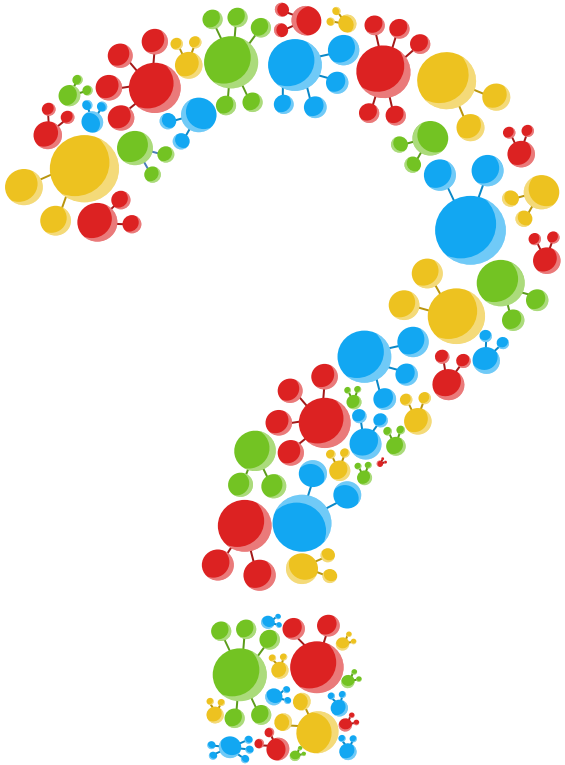
- Protocol directs collection of efficacy endpoints
  - Statement of Endpoint & Statistical Methods to assess

The between group comparison of the proportion of subjects achieving an increase in Hgb of ≥1.0 g/dL at any time point between baseline and the end of the 16-week study will be the primary endpoint. This primary efficacy variable will be analyzed using the chi-square test.

  - Secondary & Exploratory Endpoints may be given
  - When to measure?
    - At specific time points expected to show an effect

The Label & the NDA / BLA

- Draft labeling submitted: “Annotated label”
- Finalized with FDA during NDA review, just prior to product approval
- Changes may occur at any time over the life of the approved product
  - New efficacy or safety data
  - New formulations
  - New indication approvals
  - New medical science findings
  - New drug-class findings



Thank You

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