ICH M11 Digital Clinical Protocol

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Center for Biologics Evaluation and Research

U.S. Food and Drug Administration

ICH M11 Rapporteur

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FDA Disclaimer

The views and opinions presented here represent my views should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

ICH M11
Clinical electronic Structured Harmonised Protocol

- **Guideline is a high-level document that:**
  - Provides the background on why a harmonized clinical protocol template is needed, and
  - Describes design principles on how the template & technical specification were developed.
- **Template**
  - Includes identification of headers, common text, instructions, data fields and terminologies.
- **Technical Specification**
  - Serves as a technical representation of the ICH M11 protocol template to support the exchange of protocol information.
  - Basis of requirements for a M11 protocol data model.

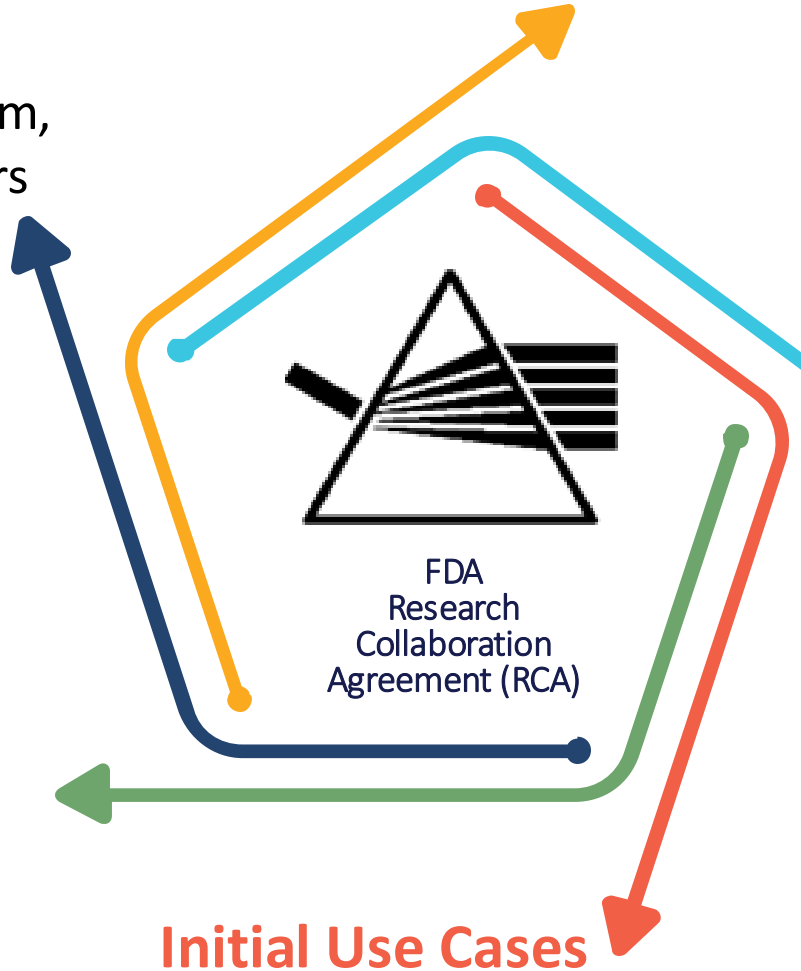
Project PRISM and M11 Use Case

Sponsors

Bayer, Boehringer Ingelheim, EMD Serono, Bristol Myers Squibb, Takeda

What is it?

A research collaboration and proof of concept project utilizing FDA's production regulatory cloud platform, precisionFDA (pFDA)

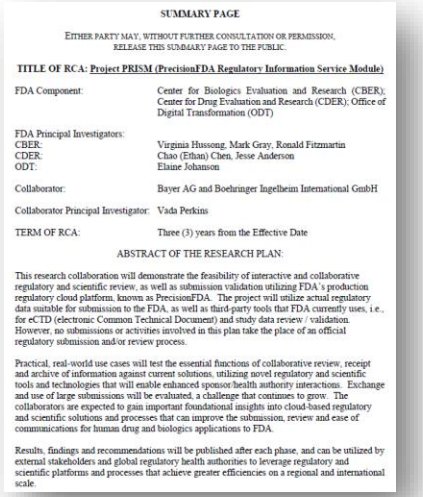


Principal Investigators

RCA principal investigators include CBER, CDER and ODT.

Who started it?

Proposed to FDA by industry companies



SUMMARY PAGE

EITHER PARTY MAY, WITHOUT FURTHER CONSULTATION OR PERMISSION, RELEASE THIS SUMMARY PAGE TO THE PUBLIC.

TITLE OF RCA: Project PRISM (PrecisionFDA Regulatory Information Service Module)

FDA Component:	Center for Biologics Evaluation and Research (CBER); Center for Drug Evaluation and Research (CDER); Office of Digital Transformation (ODT)
FDA Principal Investigators:	
CBER:	Virginia Hussong, Mark Gray, Ronald Fitzmartin
CDER:	Chao (Ethan) Chen, Jesse Anderson
ODT:	Elaine Johanson
Collaborator:	Bayer AG and Boehringer Ingelheim International GmbH
Collaborator Principal Investigator:	Vada Perkins
TERM OF RCA:	Three (3) years from the Effective Date

ABSTRACT OF THE RESEARCH PLAN:

This research collaboration will demonstrate the feasibility of interactive and collaborative regulatory and scientific review, as well as submission validation utilizing FDA's production regulatory cloud platform, known as PrecisionFDA. The project will utilize actual regulatory data suitable for submission to the FDA, as well as third-party tools that FDA currently uses, i.e., for eCTD (electronic Common Technical Document) and study data review / validation. However, no submissions or activities involved in this plan take the place of an official regulatory submission and/or review process.

Practical, real-world use cases will test the essential functions of collaborative review, receipt and archive of information against current solutions, utilizing novel regulatory and scientific tools and technologies that will enable enhanced sponsor/health authority interactions. Exchange and use of large submissions will be evaluated, a challenge that continues to grow. The collaborators are expected to gain important foundational insights into cloud-based regulatory and scientific solutions and processes that can improve the submission, review and ease of communications for human drug and biologics applications to FDA.

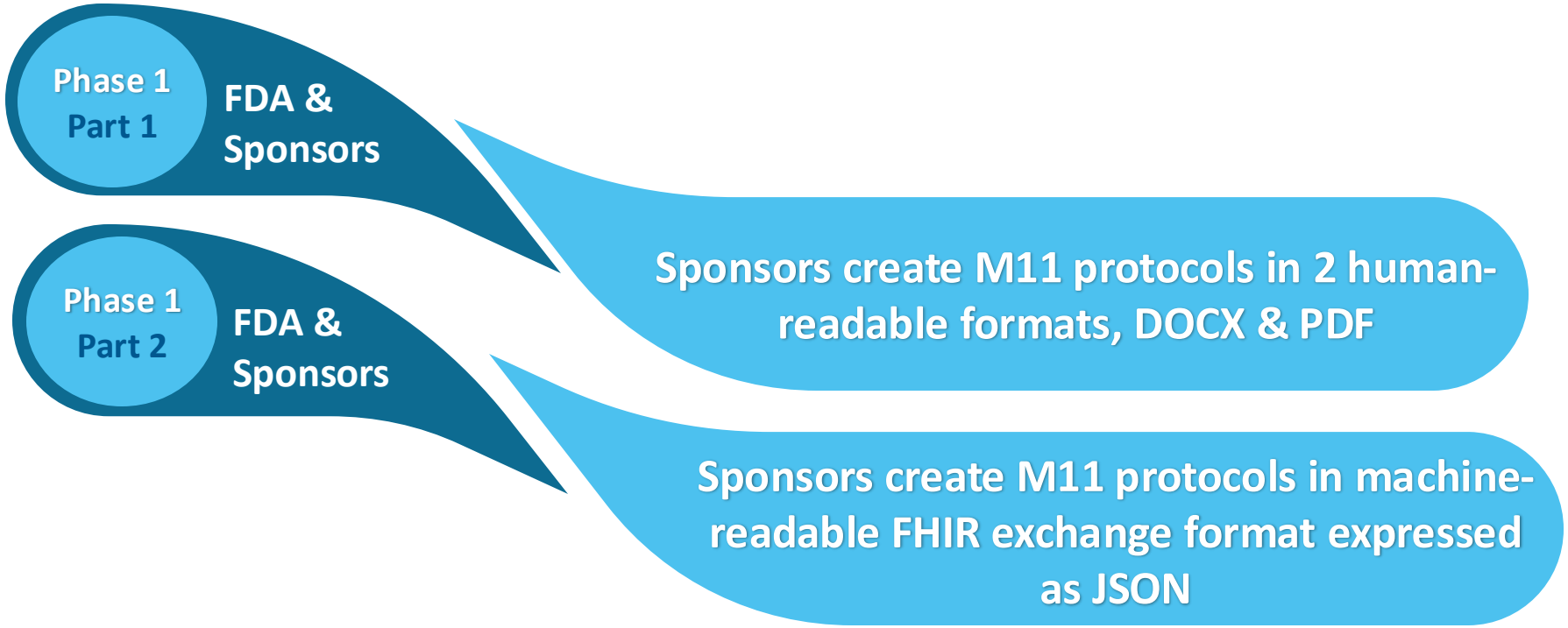
Results, findings and recommendations will be published after each phase, and can be utilized by external stakeholders and global regulatory health authorities to leverage regulatory and scientific platforms and processes that achieve greater efficiencies on a regional and international scale.

Initial Use Cases

Demonstrate the feasibility of collaborative & interactive review, as well as submission validation.

PRISM M11 Use Case – Phase 1

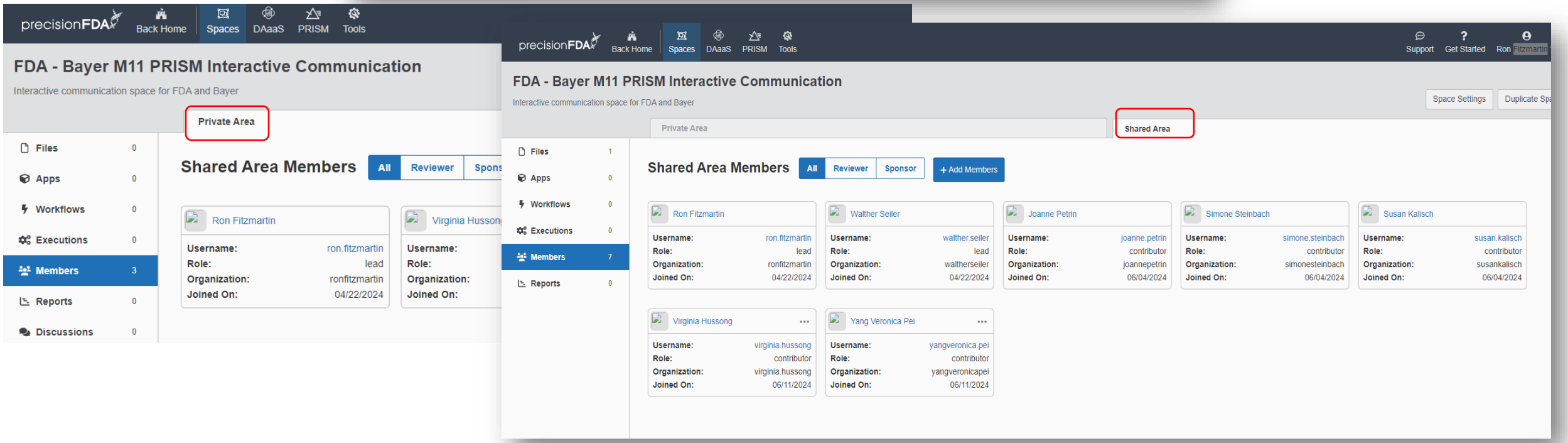
- *Demonstrate sponsor-to-regulator electronic exchange of a M11-compliant protocol and conduct interactive communication*



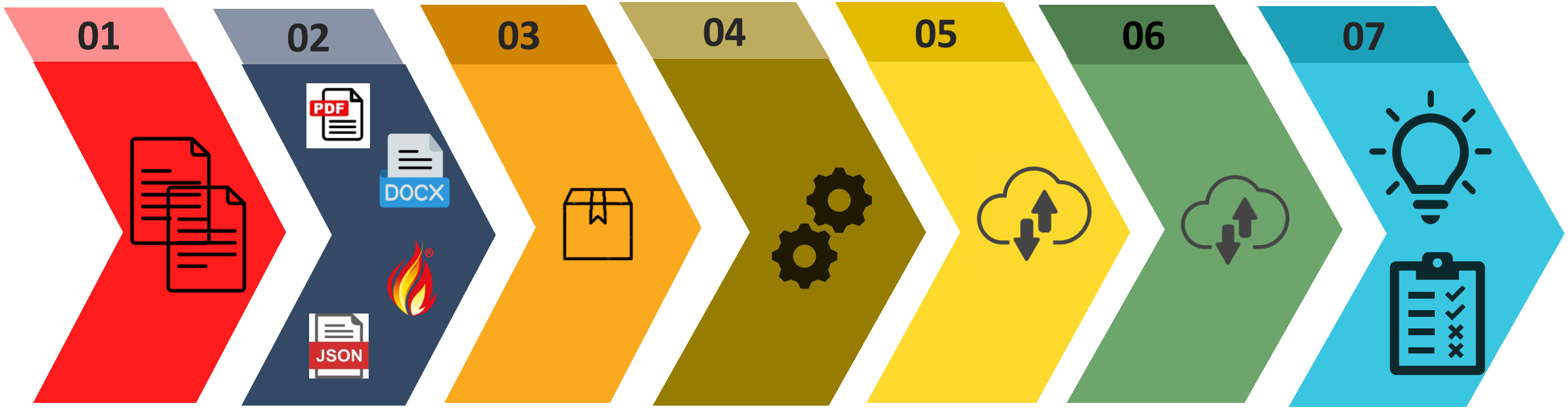
- *Results will inform the ICH M11 EWG of any content and / or technical issues prior to reaching ICH Step 3 and 4*

PRISM M11 Interactive Communication Spaces on pFDA

Review	**FDA - BMS M11 PRISM Interactive Communication** Interactive Communication Space for FDA and BMS	683	Active
Review	**FDA - Takeda M22 PRISM Interactive Communication** Interactive communication space for FDA and Takeda	681	Active
Review	**FDA - Boehringer Ingelheim M11 PRISM Interactive Communication** Interactive communication space for FDA and Boehringer Ingelheim	679	Active
Review	**FDA - Bayer M11 PRISM Interactive Communication** Interactive communication space for FDA and Bayer	677	Active



PRISM M11 Use Case Process Steps



01	02	03	04	05	06	07
Sponsors create M11 clinical protocols	Generate two human-readable & machine-readable formats	Sponsors prepare meeting package	Sponsors upload meeting pkg to pFDA Private Space	Sponsors copy pkg to FDA-Sponsor shared Space	FDA copies Sponsor pkgs to FDA private Space	Interactive Bilateral Communication

PRISM M11 Demonstration Use Case Outcomes

3. Gain knowledge

On the ease of use of the template's instructional material.

2. Exchange of protocols

Using both **human and machine- readable** formats: DOCX, PDF, and JSON, FHIR

4. Evaluation of PrecisionFDA

And potential for FDA-Sponsor interactive communication in the cloud

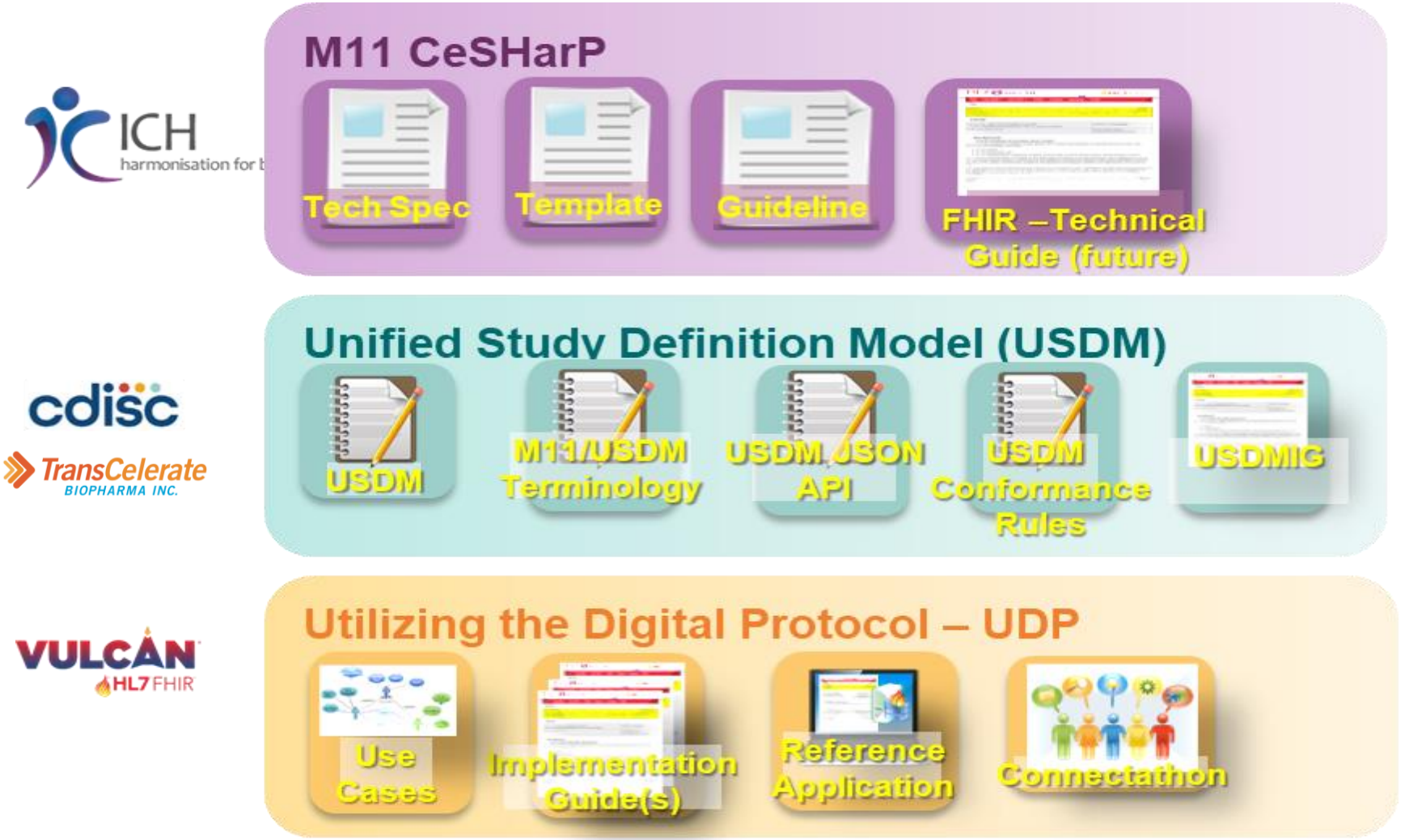
1. Preparation of M11 compliant protocols

Early Stage and Late-Stage Protocols

5. Inform FDA

On future uses of a data-driven protocol.

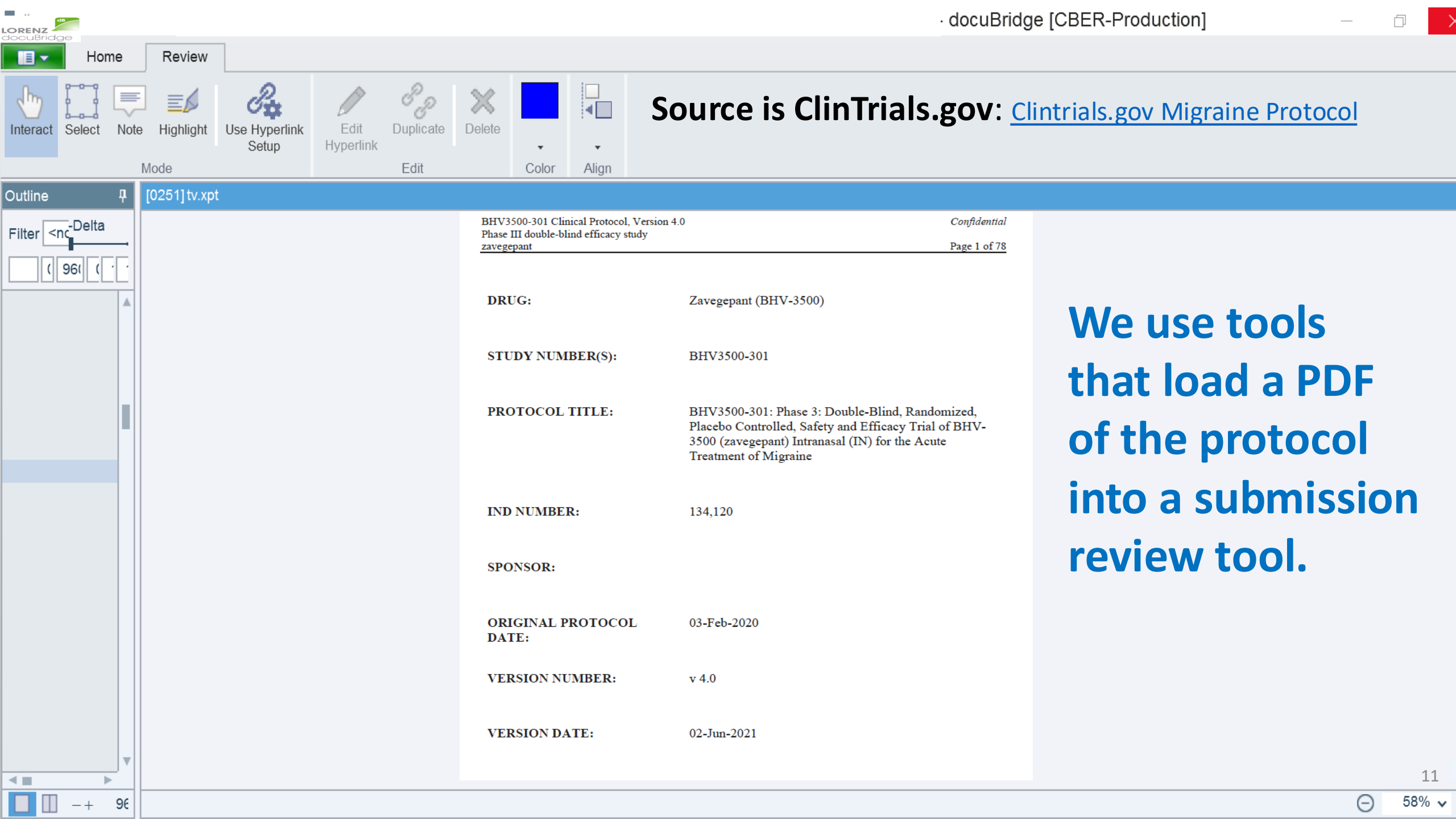
Collaboration Delivers the Digital Protocol



Imagine the future state where…

…the protocol is driven by a common data model that enables limitless personalized views of the protocol.

…For now, all we have is this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Review
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Source is ClinTrials.gov: Clintrials.gov Migraine Protocol
Outline
[0251] tv.xpt
BHV3500-301 Clinical Protocol, Version 4.0
Phase III double-blind efficacy study
zavegepant
Confidential
Page 1 of 78
DRUG: Zavegepant (BHV-3500)
STUDY NUMBER(S): BHV3500-301
PROTOCOL TITLE: BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
IND NUMBER: 134,120
SPONSOR:
ORIGINAL PROTOCOL DATE: 03-Feb-2020
VERSION NUMBER: v 4.0
VERSION DATE: 02-Jun-2021
We use tools that load a PDF of the protocol into a submission review tool.
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STUDY SUMMARY (SYNOPSIS)

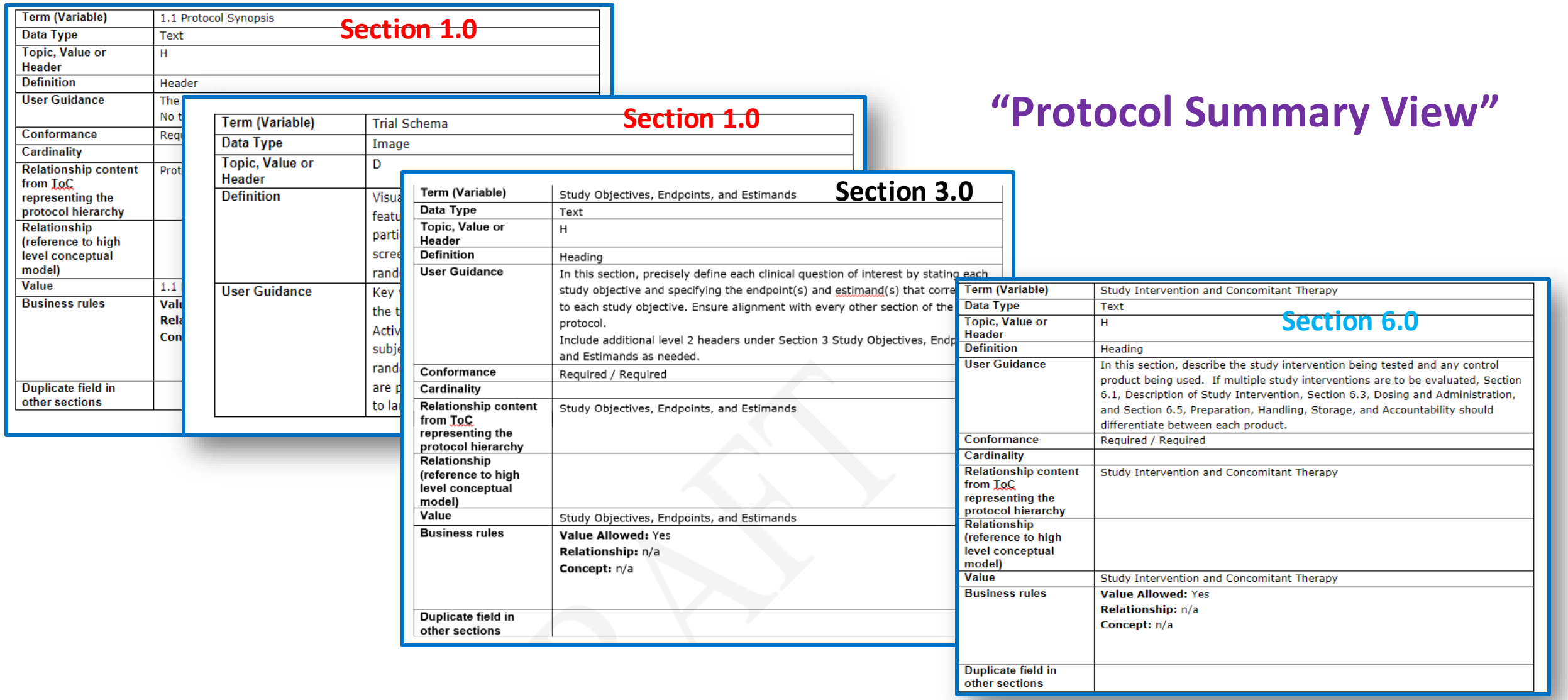
Title:	BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
Rationale:	Zavegepant is being developed for the acute treatment of migraine. Effectiveness against migraine was demonstrated in BHV3500-201, a fully powered, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study of zavegepant 5 mg, 10 mg, and 20 mg via intranasal (IN) administration. The data from this study will allow characterization of the relative safety and efficacy of IN zavegepant versus placebo in the acute treatment of moderate or severe migraine measuring freedom from pain and freedom from most bothersome system (nausea, photophobia or phonophobia) as reported just prior to treatment of the migraine. Information regarding time to onset of action, the duration of action, and the sustainability of pain freedom in subjects with migraine will also be obtained.
Target Population:	The study will recruit male and female subjects 18 years of age and older with at least a 1-year history of migraine (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders 3rd edition[1], including an age of onset prior to 50, migraine attacks that last about 4-72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month.
Number of Subjects:	Approximately 1,750 subjects will be screened to randomize approximately 1,400 subjects (approximately 700 per treatment group). Subjects will be randomized in a 1:1 ratio to the zavegepant or placebo treatment groups. Randomization will be stratified by prophylactic migraine medication use (yes or no).
Primary Objective:	To compare the efficacy of zavegepant with placebo in the acute treatment of migraine, as measured by co-primary endpoints of pain freedom at 2 hours postdose, and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose.
Secondary Objectives:	1. To compare zavegepant with placebo for pain relief at 2 hours postdose. 2. To compare zavegepant with placebo for return to normal function at 2 hours postdose according to the Functional Disability scale.

Page by page, hyperlinking back and forth

Forced into a document-centric view

M11 will break the “document-centric” protocol paradigm

M11 will Enable the Digital Clinical Protocol



"Protocol Summary View"

Source: M11 Technical Specification, ICH Step 2a/2b version

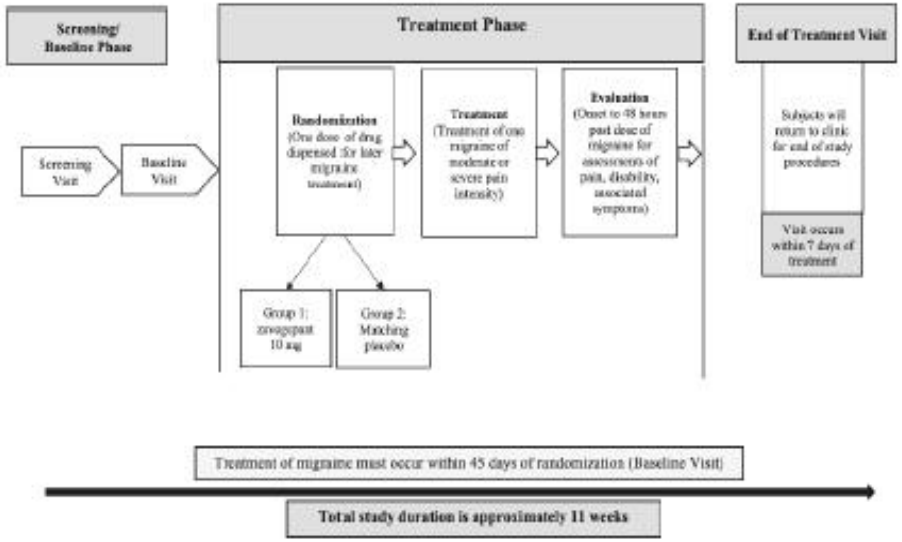
PHASE 3: DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, SAFETY AND EFFICACY TRIAL OF BHV-3500 (ZAVEGEPANT) INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE

Overall Design

Intervention Model:	[Parallel]	**Population Type:**	[Adult Participants]
Control Type:	[Placebo]	**Population Diagnosis or Condition:**	[Migraine]
Control Description:	[NA]	**Population Age:**	Minimum: 18 years Maximum: 80 years
Intervention Assignment Method:	[Stratified Randomization]	**Site Distribution and Geographic Scope:**	[Multicentre] [Multiple Countries]
Adaptive Trial Design:	[No]	**Master Protocol Design:**	[No]
Drug/Device Combination Product Indicator:	[No]		

Number of Arms	[2]
Trial Blind Schema	[Triple]
Blinded Roles	[Participant] [Investigator] [Care Provider]
Number of Participants	[1400] / [1750]
Duration	[45] [days]
Independent Committee	[No]

Trial Schema



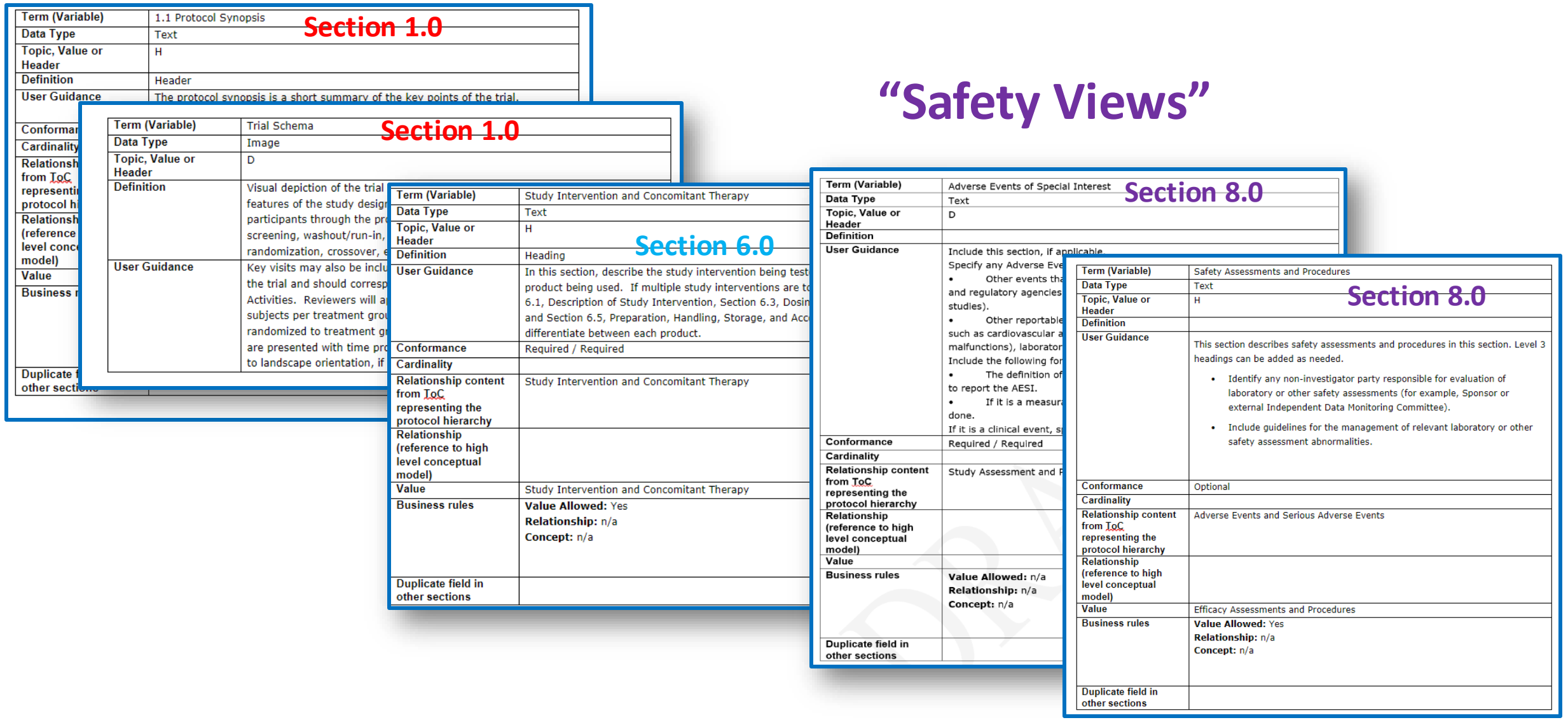
Overview of Trial Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Form	Unit Dose Strength	Dosage Level	Route of Administration	Regimen Treatment Period
Experimental	[Active]	[Zavegepant]	[Drug]	[Spray]	[mg]	[10]	[Intranasal]	[45] [days]
Placebo Comparator	[Placebo]	[Placebo]	[Drug]	[Spray]	[mg]	[10]	[Intranasal]	[45] [days]

Trial Objectives and Associated Estimands

Estimand Characteristic	Description
Population	(<The study will recruit male and female subjects 18 years of age and older with at least a 1-year history of migraine (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders 3rd edition1, including an age of onset prior to 50, migraine attacks that last about 4-72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month. >)
Treatment	(<zavegepant 10 mg via intranasal (IN) administration>)
Endpoint	(< Pain freedom at 2 hours postdose will be assessed using the percentage of subjects with a pain intensity of none at 2 hours postdose. Pain intensity will be measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe). >)
Population-Level Summary	(< Treatments compared using a Cochran-Mantel Haenszel test to estimate the difference in percentages of subjects achieving the endpoint response criteria (zavegepant-placebo) stratified by prophylactic migraine medication use at randomization (yes or no)>)
Intercurrent Event	(Strategy)
Rescue Medication	(<(The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication will be classified as failures for all efficacy assessments that are reported at or after taking rescue medication. The RM=F method will apply to all endpoints listed below, except the secondary endpoint of rescue medication use within 24 hours postdose)>)

M11 will Enable the Digital Clinical Protocol



M11 Technical Specification, Step 2a/2b version

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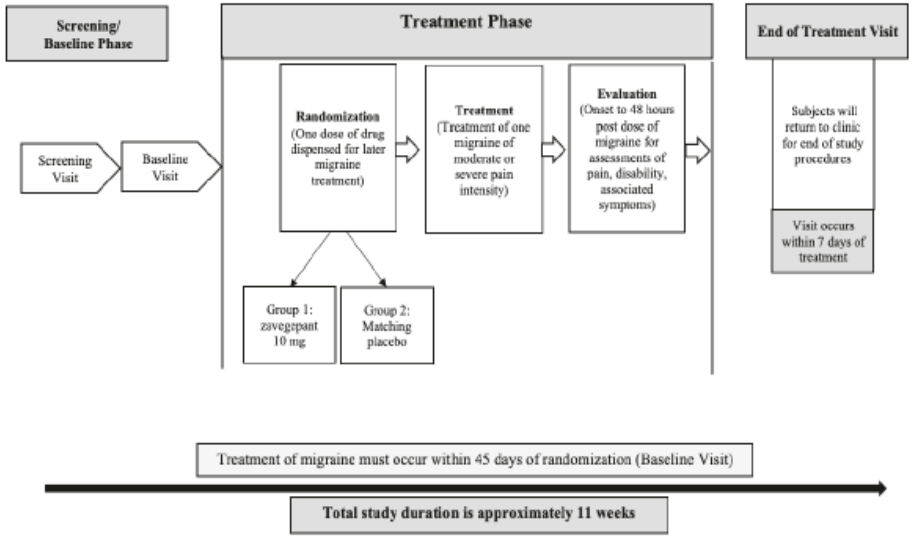


Adverse Events of Special Interest

< ***Non-serious Adverse Events***

A ***non-serious AE*** is an AE not classified as serious.

·*Collection and Reporting of Non-Serious Adverse Events*

The collection of non-serious AE information should begin at the Baseline Visit through the EOT Visit.

Non-serious AEs should be followed until conclusion or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment.

Laboratory Test Abnormalities

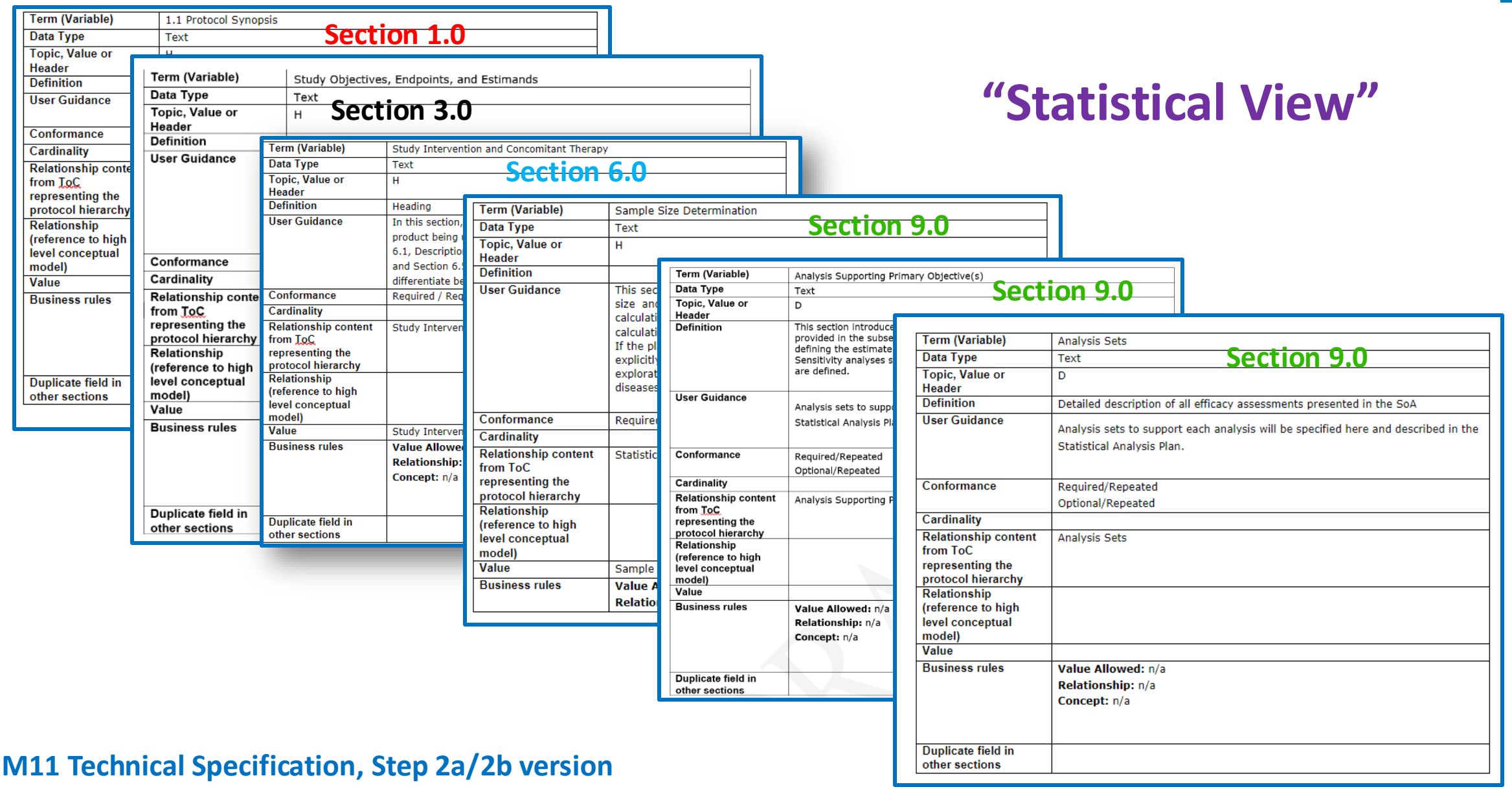
The following laboratory test abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

1. Any laboratory test result that is clinically significant or meets the definition of an SAE;
2. Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted;
3. Any laboratory abnormality that required the subject to receive specific corrective therapy.

Safety Assessments and Procedures

Procedure	Screening Visit	Baseline Randomization Visit (Day1)	Moderate or Severe Migraine Before Study Drug Administration	Post Study Drug Administration: 15, 30, 45, 60 & 90 minutes 2, 3, 4, 6, 8, 24 & 48 hours	End of Treatment Visit
Physical Examination	X				X
Nasal Inspection	X	X			X
Vital Signs / Physical Measurements	X	X			X
Adverse Event and Serious Adverse Event Assessment	X	X	X	X	X
Sheehan Suicidality Tracking Scale	X	X			
ECG	X				
Clinical Safety Laboratory Testing	X				
Liver Function Tests	X				
Lipid Panel	X				
FSH, if Applicable	X				
Pregnancy Test	X				
Urinalysis Test	X	X	X		X
Urine Drug Screen for Drugs of abuse	X				X

M11 will Enable the Digital Clinical Protocol



"Statistical View"

M11 Technical Specification, Step 2a/2b version

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Rescue Medication	{<{The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication will be classified as failures for all efficacy assessments that are reported at or after taking rescue medication. The RM=F method will apply to all endpoints listed below, except the secondary endpoint of rescue medication use within 24 hours postdose}>}

Sample Size Determination

It is anticipated that about 90% of the 700 subjects randomized to each treatment group will have a headache in the allotted time period, resulting in approximately 630 subjects evaluable for efficacy in each treatment group.

The sample size calculation is based on results from the Phase 2/3 dose-ranging study BHV3500-201. A total sample size of 1,260 evaluable subjects (630 per group) will provide approximately 91% power for the co-primary endpoint of pain freedom at 2 hours post dose, approximately 88% power for the co-primary endpoint of MBS freedom at 2 hours post dose, and approximately 80% power to detect a difference between treatment groups for both endpoints jointly.

Analysis Sets

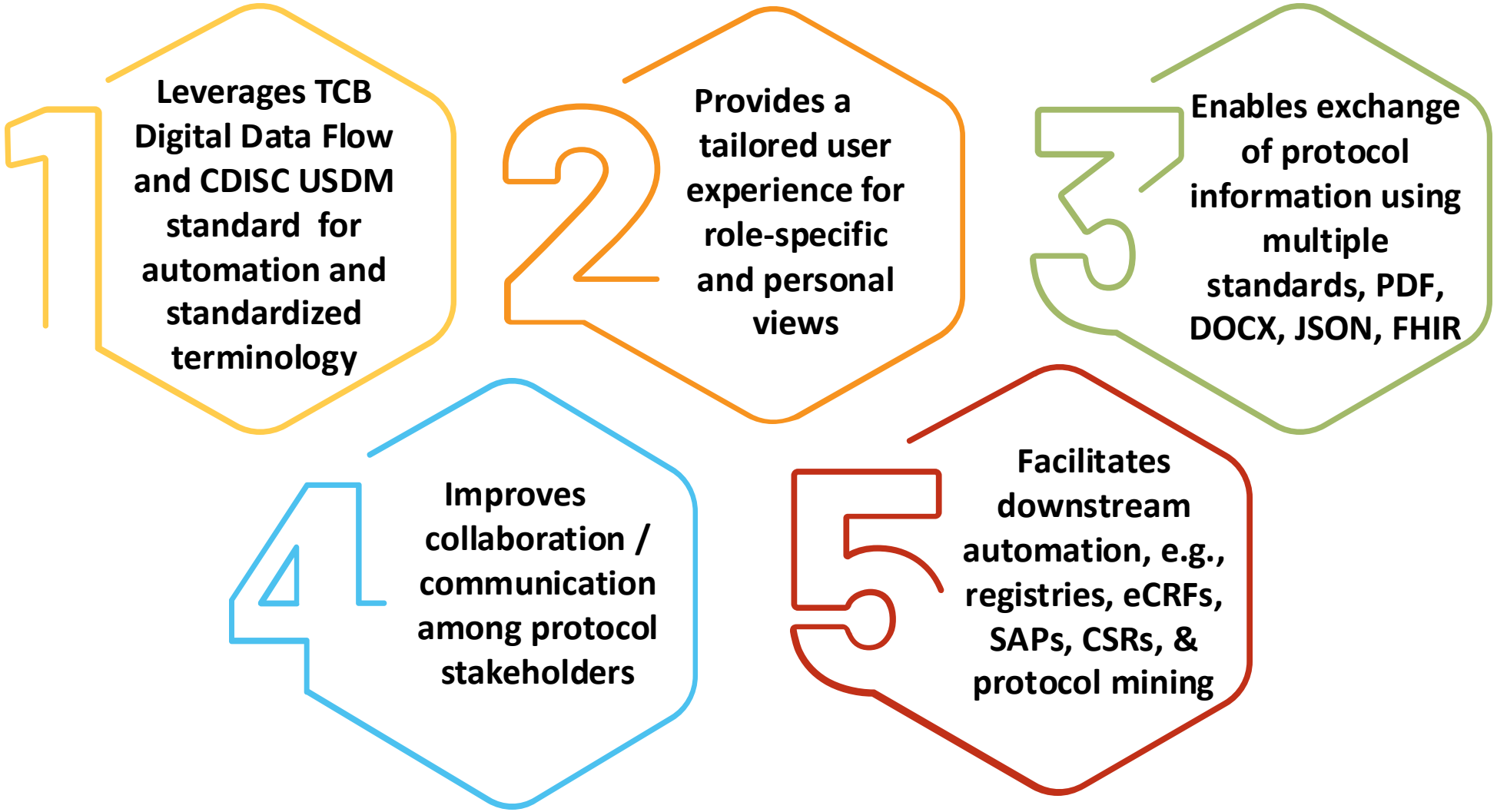
Enrolled: Subjects who sign informed consent and are assigned a subject identification number.

- **Randomized**: Subjects in the enrolled analysis set who receive a randomized treatment group assignment (zavegepant or placebo) from TWRS.
- **Safety**: Subjects in the enrolled analysis set who take study drug (zavegepant or placebo).
- **Efficacy**: Subjects in the randomized analysis set who: (1) are randomized only once; (2) have a migraine of moderate or severe intensity at the time of dosing (3) take study drug; and (4) have post-dose efficacy data.

Analysis Associated with the Primary Objective

Zavegepant will be tested for superiority against placebo at an alpha=0.05 level for both co- primary endpoints using the efficacy analysis set. For each endpoint, treatment groups will be compared using a Cochran-Mantel Haenszel test to estimate the difference in percentages of subjects achieving the endpoint response criteria (zavegepant - placebo) stratified by prophylactic migraine medication use at randomization (yes or no). The percentage of subjects achieving the endpoint response criteria will be presented with a 95% confidence interval (CI) by treatment group.

PRISM M11 Protocol Use Case - Key Points



Thank You

Ronald.Fitzmartin@fda.hhs.gov