Use case: A custom domain for induced pain, going from Source to SDTM to ADaM

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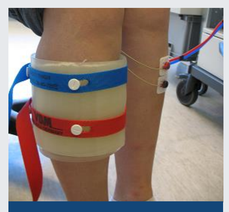
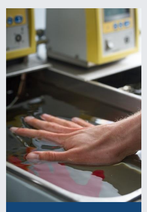
Introduction

What do you do when you want to test the analgesic effect of a novel study drug?
→ Induce pain in health volunteers

Paincart®: Comprehensive battery of tests to assess the efficacy of analgesic compounds by administering a wide variety of pain stimuli including thermal, electrical, chemical and mechanical pain.

Test	Pain Stimulus	Domain/Mechanism/Receptor Tested
Thermal Pain	Thermode	TRPV1 (>42°C, capsaicin) TRPV2 (>53°C)
Electrical Pain – Single	Transcutaneous Electrodes	By-Pass Nociceptors
Electrical Pain – Multiple	Transcutaneous Electrodes	Central Summation/Wind-Up
Tourniquet Pain	Pneumatic Pressure	Deep Muscle Nociceptors
Cold Pressor	Cold Water Bath (1°C)	TRPV3 (<17°C)
Inhibitory Conditioned Pain Modulation	Alternating between Cold Pressor Test and Electrical Pain Test	Supraspinal Inhibitory Control over Ascending Pain Stimuli
Capsaicin-Induced Hyperalgesia	Topical Capsaicin and Thermode	Inflammation, TRPV1
UVB Hyperalgesia	UVB Irradiation and Thermode	Inflammation


Thermal Pain


Cold Pain


Electrical Pain

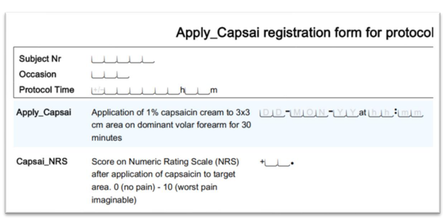
Goal:
- Reduced perception of pain with administration of novel study drug?
- Phase 1 trials might be submitted to FDA and therefore need to be converted from Source data to SDTM and ADaM

Challenges:
- No known SDTM domains to store this information
- Therapeutic Area User Guides related to patients suffering from chronic pain, while this study uses healthy subjects

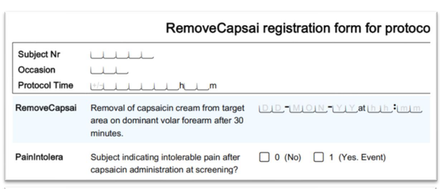
Source

Information collected on 19 different CRF forms:

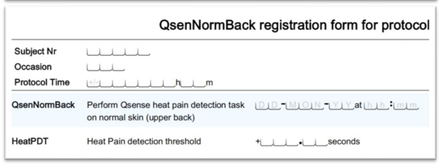
Forms for:
- Administration of Pain Agent
- Reaction to Pain Agent
- Pain Stimulus Response


Apply_Capsai registration form for protocol

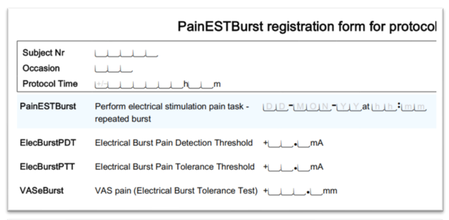
Subject Nr	
Occasion	
Protocol Time	
Apply_Capsai	Application of 1% capsaicin cream to 3x3 cm area on dominant volar forearm for 30 minutes
Capsai_NRS	Score on Numeric Rating Scale (NRS) after application of capsaicin to target area. 0 (no pain) - 10 (worst pain imaginable)


RemoveCapsai registration form for protoco

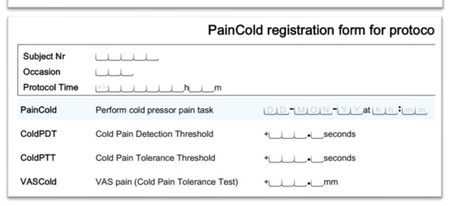
Subject Nr	
Occasion	
Protocol Time	
RemoveCapsai	Removal of capsaicin cream from target area on dominant volar forearm after 30 minutes.
PainIntolera	Subject indicating intolerable pain after capsaicin administration at screening? 0 (No) 1 (Yes. Event)


QsenNormBack registration form for protocol

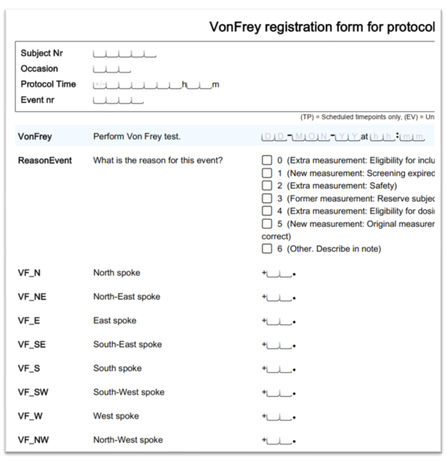
Subject Nr	
Occasion	
Protocol Time	
QsenNormBack	Perform Qsense heat pain detection task on normal skin (upper back)
HeatPDT	Heat Pain detection threshold


PainESTBurst registration form for protocol

Subject Nr	
Occasion	
Protocol Time	
PainESTBurst	Perform electrical stimulation pain task - repeated burst
ElecBurstPDT	Electrical Burst Pain Detection Threshold
ElecBurstPTT	Electrical Burst Pain Tolerance Threshold
VASeBurst	VAS pain (Electrical Burst Tolerance Test)


PainCold registration form for protoco

Subject Nr	
Occasion	
Protocol Time	
PainCold	Perform cold pressor pain task
ColdPDT	Cold Pain Detection Threshold
ColdPTT	Cold Pain Tolerance Threshold
VASCold	VAS pain (Cold Pain Tolerance Test)

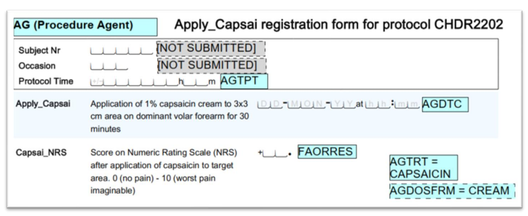

VonFrey registration form for protocol

Subject Nr	
Occasion	
Protocol Time	
Event nr	
VonFrey	Perform Von Frey test.
ReasonEvent	What is the reason for this event? 0 (Extra measurement: Eligibility for inclu; 1 (New measurement: Screening expirec; 2 (Extra measurement: Safety); 3 (Former measurement: Reserve subjec; 4 (Extra measurement: Eligibility for dosi; 5 (New measurement: Original measurer correct); 6 (Other. Describe in note)
VF_N	North spoke
VF_NE	North-East spoke
VF_E	East spoke
VF_SE	South-East spoke
VF_S	South spoke
VF_SW	South-West spoke
VF_W	West spoke
VF_NW	North-West spoke

SDTM

Main question: What goes where?

Administration of Pain Agent: AG
Reaction to Pain Agent: FA or SR
Pain Stimuli Response: Custom domain XP

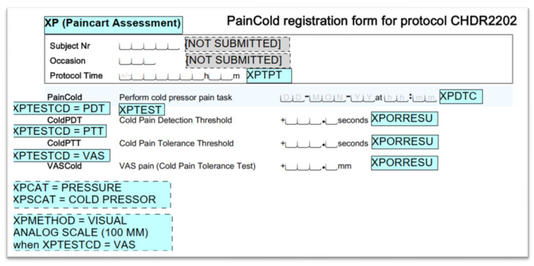

AG (Procedure Agent) — Apply_Capsai registration form for protocol CHDR2202

Subject Nr	[NOT SUBMITTED]
Occasion	[NOT SUBMITTED]
Protocol Time	AGTPT
Apply_Capsai	Application of 1% capsaicin cream to 3x3 cm area on dominant volar forearm for 30 minutes — AGDTC
Capsai_NRS	Score on Numeric Rating Scale (NRS) after application of capsaicin to target area. 0 (no pain) - 10 (worst pain imaginable) — FAORRES; AGTRT = CAPSAICIN; AGDOSFRM = CREAM


FAAG (Findings About Procedure Agents) — RemoveCapsai registration form for protocol CHDR2202

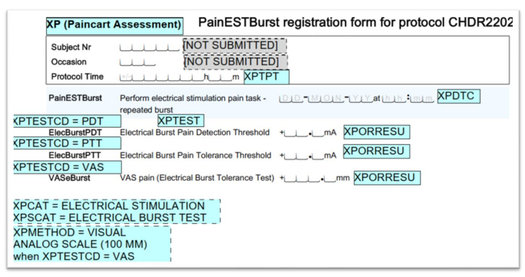
Subject Nr	[NOT SUBMITTED]
Occasion	[NOT SUBMITTED]
Protocol Time	
RemoveCapsai	Removal of capsaicin cream from target area on dominant volar forearm after 30 minutes.
PainIntolera	Subject indicating intolerable pain after capsaicin administration at screening? 0 (No) 1 (Yes. Event) — FAORRES

FATESTCD = INTOL
FATEST = Intolerable Pain After Administration
FAOBJ = CAPSAICIN TEST DOSE


XP (Paincart Assessment) — PainCold registration form for protocol CHDR2202

Subject Nr	[NOT SUBMITTED]
Occasion	[NOT SUBMITTED]
Protocol Time	XPTPT
PainCold	Perform cold pressor pain task — XPDTC
XPTESTCD = PDT	XPTEST: Cold Pain Detection Threshold — XPORRESU
XPTESTCD = PTT	ColdPTT: Cold Pain Tolerance Threshold — XPORRESU
XPTESTCD = VAS	VASCold: VAS pain (Cold Pain Tolerance Test) — XPORRESU

XPCAT = PRESSURE
XPSCAT = COLD PRESSOR
XPMETHOD = VISUAL ANALOG SCALE (100 MM) when XPTESTCD = VAS


XP (Paincart Assessment) — PainESTBurst registration form for protocol CHDR2202

Subject Nr	[NOT SUBMITTED]
Occasion	[NOT SUBMITTED]
Protocol Time	XPTPT
PainESTBurst	Perform electrical stimulation pain task - repeated burst — XPDTC
XPTESTCD = PDT	XPTEST: ElecBurstPDT: Electrical Burst Pain Detection Threshold — XPORRESU
XPTESTCD = PTT	ElecBurstPTT: Electrical Burst Pain Tolerance Threshold — XPORRESU
XPTESTCD = VAS	VASeBurst: VAS pain (Electrical Burst Tolerance Test) — XPORRESU

XPCAT = ELECTRICAL STIMULATION
XPSCAT = ELECTRICAL BURST TEST
XPMETHOD = VISUAL ANALOG SCALE (100 MM) when XPTESTCD = VAS

ADaM

From the SAP the ADXP needs to contain:
Change from baseline of measurements within 48 hours after dosing for:

- Pressure Pain (PDT, PTT and VAS)
- Heat Pain (PDT and VAS)
- Cold Pressor (PDT, PTT and VAS)
- Electrical Stair Test (PDT, PTT and VAS)
- Electrical Burst Test (PDT, PTT and VAS)
- Conditioned Pain Modulation (PDT and PTT)
  = Change from electrical stair pain pre- and post-cold pressor

3.1.2 Conditioned Pain Modulation (CPM) Response

Conditioned pain modulation (CPM) response is quantified by calculating the difference of pain detection (PDT) and pain tolerance threshold (PTT) of the electrical stair pain test, directly after the cold pressor pain test, and the electrical stair pain detection and tolerance thresholds prior to the cold pressor pain test.

- Conditioned Pain Modulation Response based on PDT = electrical stair measure post-cold pressor – electrical stair measure prior cold pressor
- Conditioned Pain Modulation Response based on PTT = electrical stair measure post-cold pressor – electrical stair measure prior cold pressor

The calculation is done only when electrical stair measure is done within 5 min after the cold pressor test. Otherwise it is set to missing.

Challenges with creation of custom domain: XP

Creation of correct categories

XPCAT	Set to "HEAT PAIN" when CRF form contains "Qsen". Otherwise, set to "PRESSURE" when CRF form contains "PainCold" or "PainPressure". Otherwise, set to "ELECTRICAL STIMULATION" when CRF form contain "EST". Otherwise set to "VON FREY" when CRF form contains "VF" or "VonFrey".
XPSCAT	Set to "COLD PRESSOR" when CRF form contains "PainCold". Otherwise, set to "ELECTRICAL BURST TEST" when CRF form contains "Burst". Otherwise, set to "ELECTRICAL STAIR TEST" when CRF form contains "Stair". Otherwise, set to "PRESSURE PAIN" when CRF form contains "PainPressure". Otherwise, set to "CAPSAICIN SKIN" when CRF form contains "Caps". Otherwise, set to "NORMAL SKIN" when CRF form contains "Norm". Otherwise, set to "UVB BURNT SKIN" when CRF form contains "UVB". Otherwise, set to missing.

Grouping of same tests and using correct and consistent terminology

Most reactions to pain stimuli are measured as:
- Pain Detection Threshold (PDT)
- Pain Tolerance Threshold (PTT)
- Visual Analogue Scale (VAS)

CODELIST	TYPE	FROM	TO
XPTESTCD		COLDPDT	PDT
XPTESTCD		COLDPTT	PTT
XPTESTCD		VASCOLD	VAS
XPTESTCD		ELECBURSTPDT	PDT
XPTESTCD		ELECBURSTPTT	PTT
XPTESTCD		VASEBURST	VAS
XPTESTCD		ELECSTAIRPDT	PDT
XPTESTCD		ELECSTAIRPTT	PTT
XPTESTCD		VASESTAI	VAS
XPTESTCD		PRESSUREPDT	PDT
XPTESTCD		PRESSUREPTT	PTT
XPTESTCD		VASPRESS	VAS
XPTESTCD		CAPSHEATPDT	PDT
XPTESTCD		HEATPDT	PDT
XPTESTCD		UVBHEATPDT	PDT
XPTESTCD		VF_THRESHOLD	PDT
XPTESTCD		VF_N	VF_N
XPTESTCD		VF_NE	VF_NE
XPTESTCD		VF_E	VF_E

Challenges

- Creation of unique PARAMCDs

Concatenation of:
"EBT_" and XP.XPTESTCD when XP.XPSCAT contains "BURST".
"EST_" and XP.XPTESTCD when XP.XPSCAT contains "STAIR".
"C_A_" and XP.XPTESTCD when XP.XPSCAT = "CAPSAICIN SKIN" and XP.XPLOC = "VOLAR FOREARM".
"N_A_" and XP.XPTESTCD when XP.XPSCAT = "NORMAL SKIN" and XP.XPLOC = "VOLAR FOREARM".
"N_B_" and XP.XPTESTCD when XP.XPSCAT = "NORMAL SKIN" and XP.XPLOC = "UPPER BACK".
"U_B_" and XP.XPTESTCD when XP.XPSCAT = "UVB BURNT SKIN" and XP.XPLOC = "UPPER BACK".
"COLD_" and XP.XPTESTCD when XP.XPSCAT contains "COLD".
"PRES_" and XP.XPTESTCD when XP.XPSCAT contains "PRESSURE".
"CPM" and XP.XPTESTCD for Conditioned Pain Modulation derivation.

- Derivation of Conditioned Pain Modulation (CPM)
  - Making sure post electrical stair test was done within 5 minutes of cold pressor test
  - Matching pre and post electrical stair test to calculate difference
  - Creation of exclusion flag for post electrical stair test after it was used for CPM derivation
  - Merging timing variables from post electrical stair test to CPM record

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