Platform Study Monitoring

The HDClarity experience

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Study Overview

- HDClarity is a multi-site CSF and plasma collection
  - currently active in Canada, US, UK and Germany
  - sites planned in Spain, Italy, Poland, Portugal, France
- Minimum of 2 study visits, screening and sampling
  - 20ml CSF and up to 50ml plasma are collected
- Potential for repeat sampling visits
- The HDClarity PI is not necessarily the Enroll-HD PI

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HDClarity  Enroll-HD

- Enroll-HD is the platform for HDClarity
- Sites and participants must be active in Enroll-HD
- Linked EDC used for HDClarity data capture
- Enroll-HD core assessments are repeated at HDClarity screening if >2 months since Enroll-HD visit
- Enroll-HD General Forms are updated at all visits

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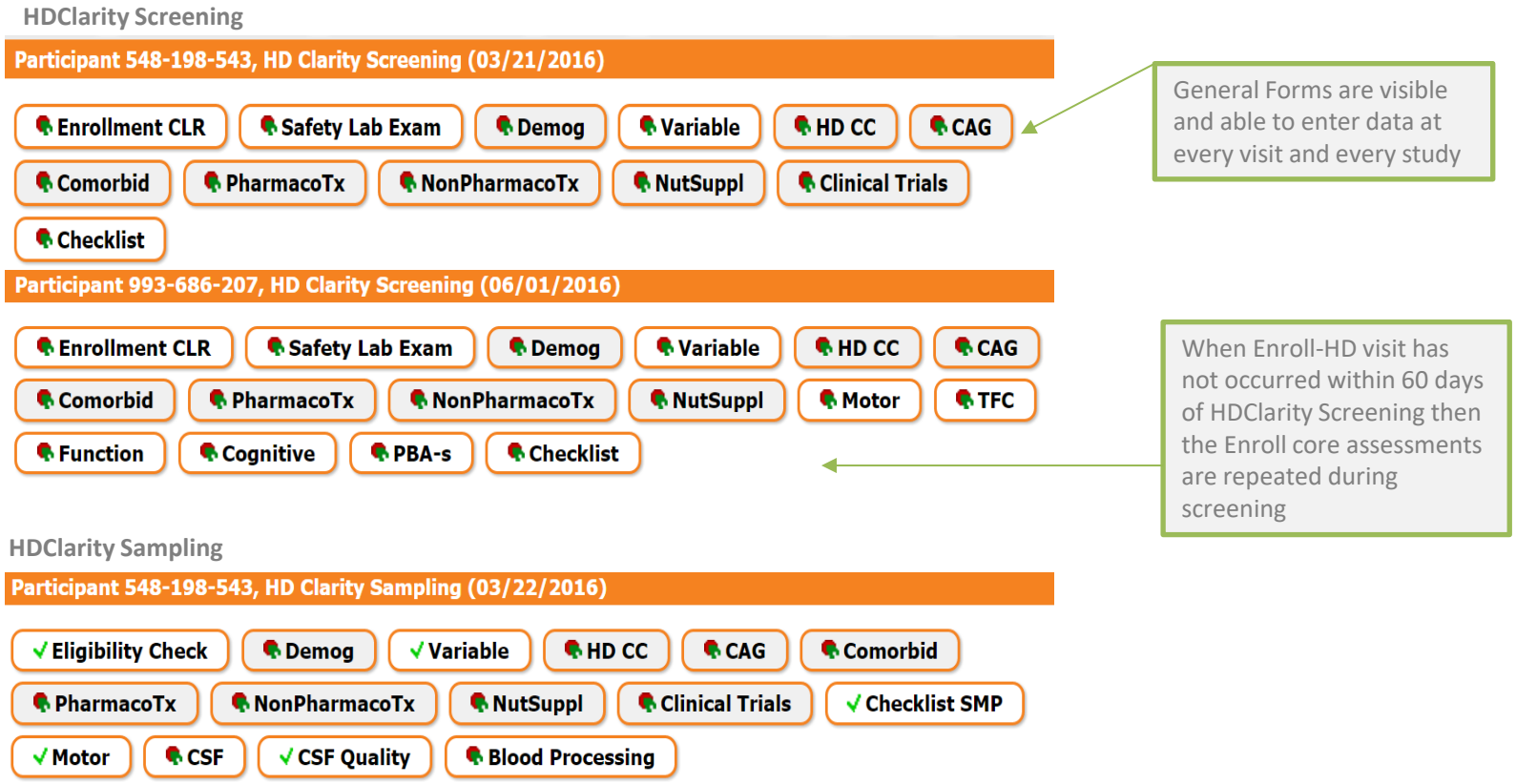
HDClarity EDC



SITE SET UP AND TRAINING

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Site selection

- The Enroll-HD team advise on site selection based on
  - known expertise and clinical trial experience
  - performance in Enroll-HD (recruitment, site issues, PVs, data entry)
  - participant population
- A site selection questionnaire then determines if the site
  - is able to deliver the protocol (e.g. rapid sample processing)
  - has access to the necessary equipment (-80 freezer, 2 centrifuges)
  - has access to a certified lab able to perform CSF cell counts

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Site set up

- When an approved ICF and site agreement are in place, HDClarity CC collect
  - PI signed protocol
  - PI signed delegation log
  - CVs and GCP for everyone on the delegation log
  - User Roles and Responsibilities Form (URRF) for EDC access
  - Calibration certificates for pipettes, centrifuges and freezer
- The HDClarity delegation log is checked with the Enroll-HD team to ensure that all raters are appropriately certified
- HDClarity CC collect medical license registration information for all clinicians that are not already in Enroll-HD

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Site initiation

- Prior to the site initiation visit (SIV), the site are given access to the HDClarity training videos on the EDC
- A study-specific investigator site file is provided
- The first biosample kits are provided
- The SIV is usually done remotely and consists of 2 parts
  - The technical SIV (sample collection and processing)
  - The non-technical SIV (e.g. recruitment, scheduling, EDC training, participant and site payment)
- Following the SIV, the site complete the HDClarity training log and are given access to the EDC training site

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STUDY EXECUTION

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Inclusion criteria

Group	Local CAG	Disease Burden	UHDRS Diagnostic Confidence	UHDRS TFC
Control	<36 (or no known family history)	-	-	-
Early Premanifest	≥ 40	< 250	< 4	-
Late Premanifest	≥ 40	≥ 250	< 4	-
Early Manifest	≥ 36	-	4	7-13
Moderate Manifest	≥ 36	-	4	4-6
Late Manifest	≥ 36	-	4	0-3

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Inclusion criteria

- If there's no local CAG available or the report does not contain allele lengths, sites must confirm eligibility with HDClarity CC
- Genotype unknown are not eligibile
- Community controls are eligible

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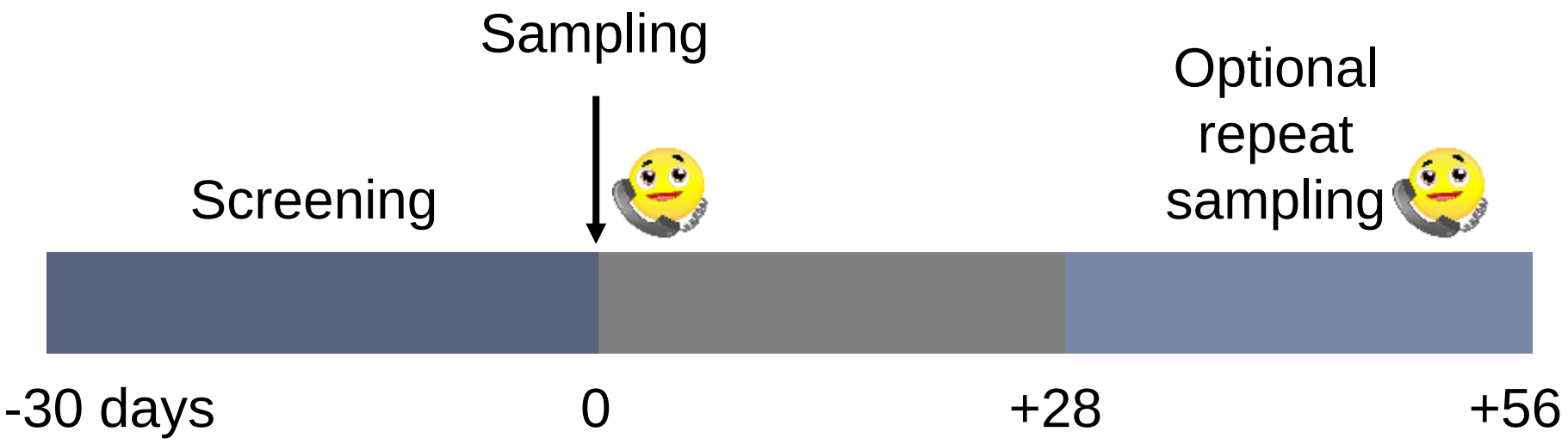
Visit frequency



Up to 3 visits within 4-8 weeks

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Definitions for reportable events

- AEs must be reported within 48 hours using the HDClarity specific AE log
  - Verbatim term describing the event (Medra)
  - Date of event
  - Severity
  - Relationship to Study
  - Final outcome
  - Expected

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Definitions for reportable events

- SAEs must be reported within 24 hours using the SAE eCRF
  - Brief description of the SAE
  - Category
  - Any medical, behavioural, or other intervention taken as a result of this SAE
  - Final outcome
  - Status of the SAE report

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Study specific waivers

- More than 60 days between the last Enroll-HD visit and the HDClarity Screening visit
- More than 30 days between the HDClarity Screening and HDClarity Sampling Visits
- Any variations to the Inclusion and/or Exclusion criteria including screening safety bloods out of range
- In addition, CI approval is required in advance for rescreening

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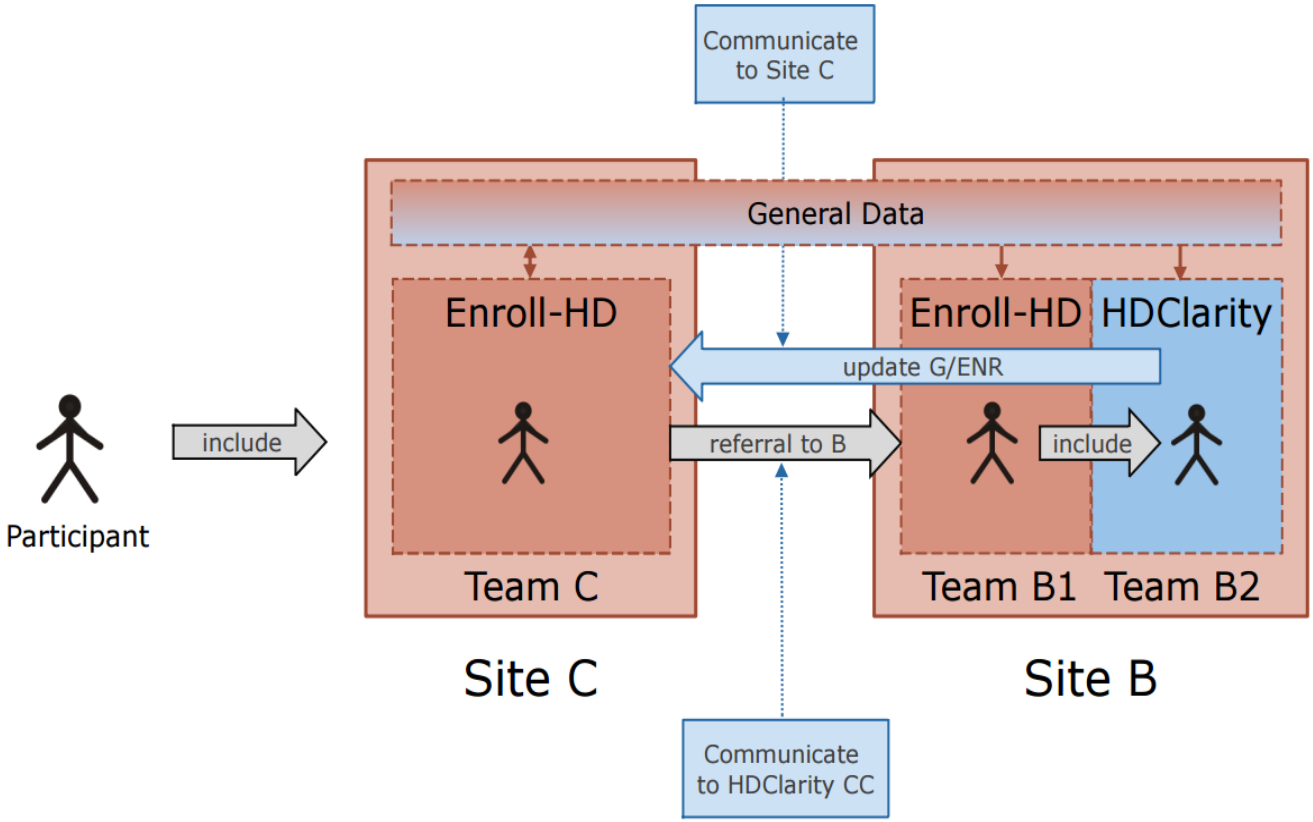
Cross-site enrollment



MONITORING

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IMV scheduling

- HDClarity IMVs are performed alongside an Enroll-HD IMV
- HDClarity Clinical Site Status Tracker is circulated weekly
  - Current recruitment
  - Site status (in set-up, open to recruitment)
- Enroll-HD inform HDClarity CC of the planned IMV scheduling
- The date of the RDR tracker request is provided
- Time allocated depends on the number of eligible visits

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During the IMV

- Review of informed consent forms
- Verify eligibility of enrolled participants
- Review HDClarity ERB/ REB/ IRB approval of revisions to ICF
- Check status of required revisions noted during previous IMV
- Continued adequacy of study staff and facilities for HDClarity
- Review of new and ongoing AEs and SAEs
- Protocol violations
- Inspect ISF
- Equipment
- Source data verification

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Source Data Verification

- Screening visit SDV
  - 100% for ICFs, inc/exc criteria, waivers, AEs
  - 50% for screening safety blood reports
  - 25% for Concomitant medications and comorbid conditions
  - 10% for Enroll-HD core assessments completed at screening
- Sampling visit
  - 100% eligibility check, waivers, AEs
  - 50% for CSF and blood collection and processing and CSF cell counts
  - 25% for Concomitant medications and comorbid conditions

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ICFs

- As a minimum requirement, ICF checks must be complete before samples can be shared
- HDClarity shipment page now includes a notification that ICF has been checked off
- HDClarity ICF monitoring form in development

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Working with central laboratories

- Laboratory staff are often not part of the clinical site team under the direction of the site PI
- Central or external labs have local SOPs for sample processing
- Only the lab manager may be named on the delegation log and is responsible for ensuring lab staff are trained on the study protocol
- Paper forms and worksheets are provided
  - Biosample processing kits are mixed
  - Implausible processing times
  - Number of samples implausible or incorrectly recorded
  - Time of storage

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Screening safety bloods

Ordercode	Description	Value	Units	Range	Flag
COAT-PT	Prothrombin Time	10.4	secs	10.0-12.0	
COAT-INR	INR	0.95			
COAT-APTT	APTT	26	secs	25-37	
COAT-APRA	APTT Ratio	0.8		0.8-1.2	
COAT-FIB	Fibrinogen	2.80	g/L	1.5-4.0	
CRP-CRP	C-reactive protein	0.9	mg/L	0-5.0	
ELU-NA	Sodium	142	mmol/L	135-145	
ELU-K	Potassium	4.6	mmol/L	3.5-5.1	
ELU-UREA	Urea	6.6	mmol/L	1.7-8.3	
ELU-CREA	Creatinine	68	umol/L	59-112	
ELU-GFR	Estimated GFR	>60			
ELU-GFR	Estimated GFR	COMMENTS: Units: mL/min/1.73sqm Multiply eGFR by 1.21 for people of African Caribbean origin. Interpret with regard to UK CKD guidelines: www.renal.org/information-resources Use with caution for adjusting drug dosages - contact clinical pharmacist for advice.			
FBCY-WCC	White cell count	6.21	x10^9/L	3.0-10.0	
FBCY-RCC	Red cell count	4.67	x10^12/L	4.4-5.8	
FBCY-HBGL	Haemoglobin (g/L)	139	g/L	130-170	
FBCY-HCTU	HCT	0.413	L/L	0.37-0.50	
FBCY-MCVU	MCV	88.4	fL	80-99	
FBCY-MCHU	MCH	29.8	pg	27.0-33.5	
FBCY-MCGL	MCHC (g/L)	337	g/L	320-360	
FBCY-RDWU	RDW	13.2	%	11.5-15.0	
FBCY-PLT	Platelet count	201	x10^9/L	150-400	
FBCY-MPVU	MPV	12.5	fL	7-13	
FBCZ-NE	Neutrophils	68.0% 4.22	x10^9/L	2.0-7.5	
FBCZ-LY	Lymphocytes	20.5% 1.27	x10^9/L	1.2-3.65	
FBCZ-MO	Monocytes	9.2% 0.57	x10^9/L	0.2-1.0	
FBCZ-EO	Eosinophils	1.8% 0.11	x10^9/L	0.0-0.4	
FBCZ-BA	Basophils	0.5% 0.03	x10^9/L	0.0-0.1	

Date of blood draw:	09	05	2017		
Results of laboratory examinations for safety	Actual		Lower limit		Upper limit
White Cell Count	6.21		3		10
Neutrophil Count	4.22		2		7.5
Lymphocyte Count	1.27		1.2		3.65
Hemoglobin (Hb)	139		130		170
Platelets	201		150		400
Prothrombin Time (PT)	10.4		10		12
Activated Partial Thromboplastin time (APTT)	26		25		37
CRP	0.9		0		5
Safety lab result:	passed				

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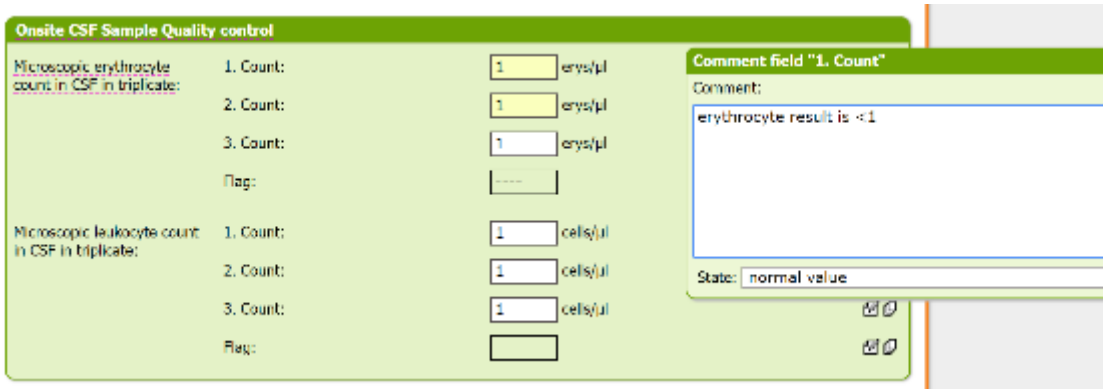
CSF cell counts

Ordercode	Description	Value	Units	Range	Flag
HCSF-NCAP	CSF Appearance	Clear Colourless Fluid			
HCSF-NCQR	CSF volume received	Approximately 1x0.3mL CSF			
HCSF-CTYP	CSF Type	Lumbar CSF			
HCSF-WCC1	CSF WCC TUBE 1	1 Lymphocyte	cu/mm		
HCSF-WCC2	CSF WCC TUBE 2	1 Lymphocyte	cu/mm		
HCSF-WCC3	CSF WCC TUBE 3	1 Lymphocyte	cu/mm		
HCSF-NCRC	CSF Red cell count	<1	cu/mm		
HCSF-NCRC	CSF Red cell count	COMMENTS: <1 <1			
HCSF-NCGL	CSF Random glucose	Cancelled - No Specimen received	mmol/L		
HCSF-NCTP	CSF Total Protein	Regret insufficient sample for analysis.	g/L		



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Protocol violations

- Ahead of the IMV, the HDClarity PV tracker is provided
  - Informed consent
  - Data protection
  - Inc/exc criteria
  - Biosamples (CSF or blood volume, samples stored incorrectly)
  - Safety (unreported S/AE, LP when safety bloods out of range)
  - Other
- Few PVs but most common are informed consent, CAG ineligibility, blood volume >50ml and AE reported >48 hours
- Need to be informed of any Enroll-HD PVs that may necessitate quarantine of HDClarity data

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IMV Reporting

- A separate report template for each platform study
- IMV follow up letter sent to site and HDClarity CC
- IMV report and PV tracker sent to HDClarity CC

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