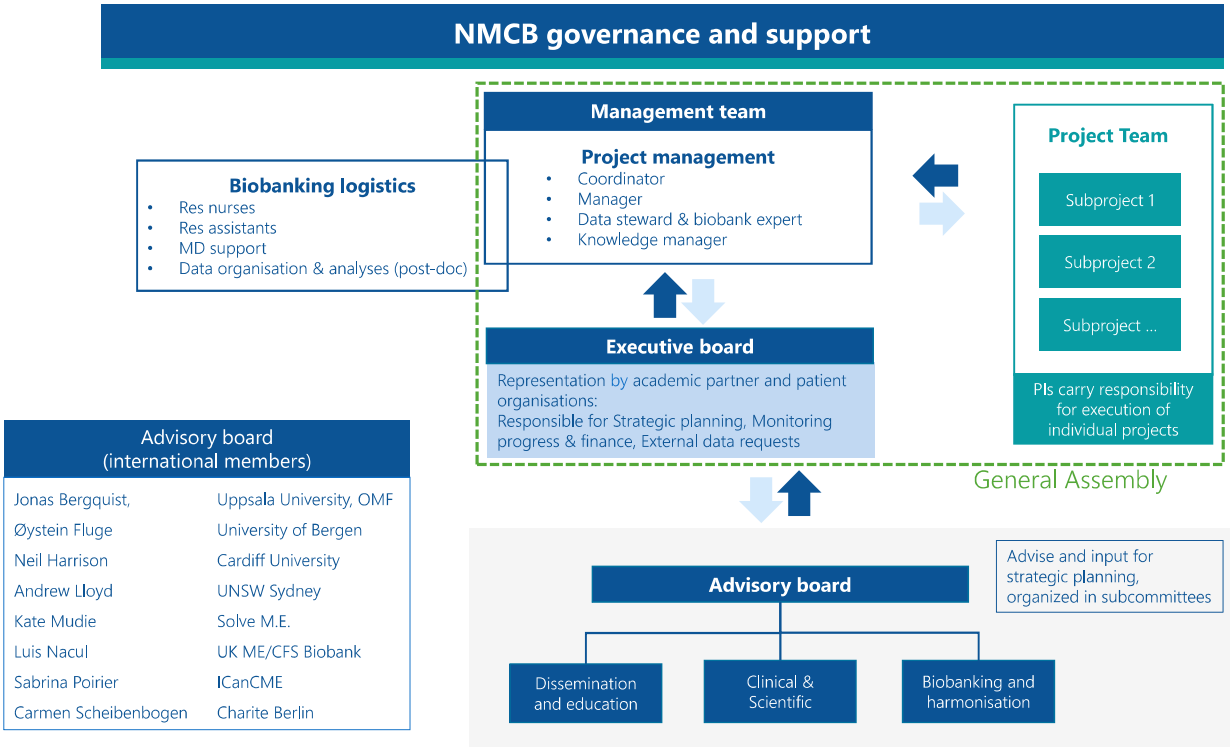

Figure 1. NMCB governance involves 4 bodies with distinct roles: The **Executive Board (EB)** is the supervisory body and responsible for overall strategy and financial planning. It is accountable for the budget, and progress and quality of deliverables. It also reviews data-access requests. Chaired by the PI/coordinator, it has rotating members, which are selected representatives of the participating research institutes and the 3 patient organisations. The **Management Team (MT)** is led by the PI/coordinator and supported by a project manager, reporting to the EB. It oversees day-to-day running of patient inclusion and biobanking (by nurses and assistants), data management (by a data steward and biobanking expert) and the realisation of impact deliverables (by a knowledge manager). The **Project Team (PT)** comprises of PI's running the (independently funded and interacting) research projects. Chaired by the Coordinator, the PT and MT collaborate closely on recruitment, (bio-)sampling and data processing. Combined the EB, MT and PT form the **General Assembly (GA)**. The GA votes on major modifications to the Consortium Agreement and implementation plan, major budget/ funding issues, and revocation or inclusion of a partner. Chaired by the PI/Coordinator it has a twice-yearly plenary meeting. The GA and its constituting bodies are supported by an International **Advisory Board (AB)**. The AB comprises of three advisory committees (AC) with a broad stakeholder representation, respectively; 1) dissemination & education; 2) clinical & research; 3) biobanking & harmonisation. Members are appointed for 2 years and composition may vary depending on consortium needs.

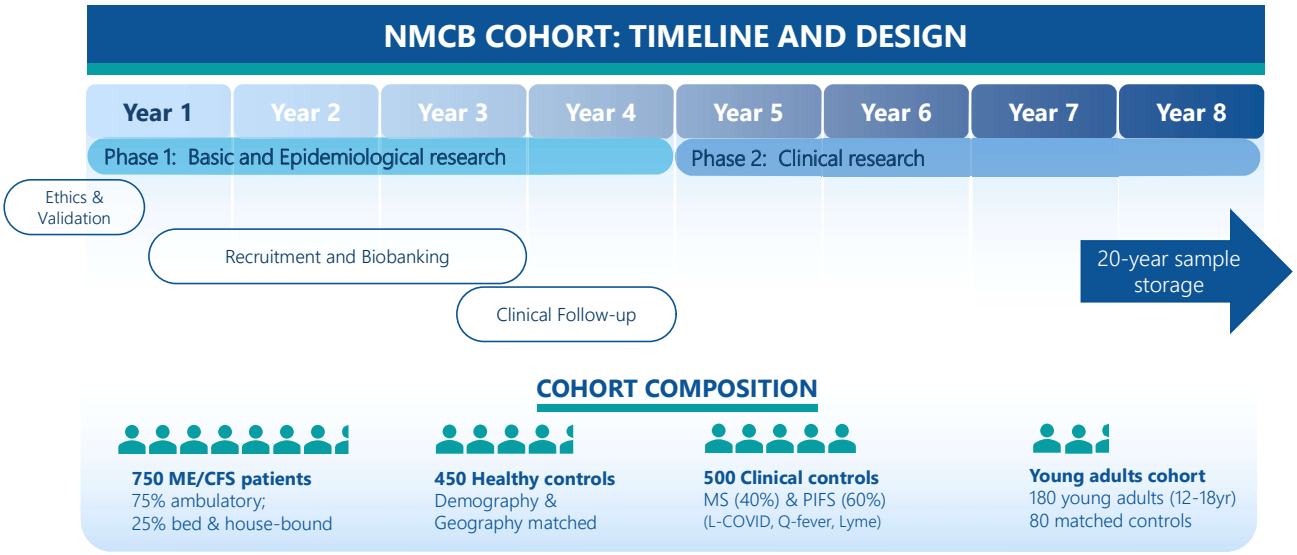

Figure 2: ME/CFS patients (N=750) will be recruited primarily via support of patient organizations and clinical centers. A home visit program will facilitate inclusion of house and bed-bound patients (inclusion target 25%). Sex and age-matched Healthy Controls (N=450) are recruited from the same area and social strata. Disease controls (N=500, 40% Multiple Sclerosis, 60% PIFS patients) are recruited from longitudinal studies whereby participants gave permission for follow-up (see **Table 1**). A second on-line assessment is planned for months 30-46 (symptoms and health status, living conditions, update contact details). A subset (N=400) will undergo a repeat home-visit (in year 4) to replenish biobank samples.

An adolescent / young-adult ME/CFS registry and biobank (60 patients, 20 controls; aged 12 - 18 years) is already in existence (described in a separate application; PI dr N. Eijkelkamp) and will be incorporated into the NMCB data base. This biobank will be expanded passively through patient inflow to the Wilhelmina Children's Hospital, approximating 180 patients and 80 controls at the end of year 3.

Table 1: Overview of primary PIFS and MS cohorts. PIFS participants will be screened (using the DSQ-short form[9]) and invited to participate if they meet a ME/CFS case definition.

Disease	Study	Start-End inclusion, follow-up assessment	N	Biosamples	Case rate CDC-94 / Severe fatigue
Lyme borreliosis	LymeProspect study Vrijmoeth 2019, BMC Infect Dis; Ursinus 2021 Lancet RHE	**2015-2018**, ongoing	1,135	Plasma, serum, GWAS	27%
COVID-19	LongCovid study RIVM Mutubuki 2022, preprint medRxiv	**2021**, ongoing	15,000 prospective 7,000 retrospectve		prospective 10% retrospectieve 40%
COVID-19	VIS/RECoVERED Wynberg, CID 2021	**2020-2021**, ongoing	349 longitudinal	Plasma/serum, PBMC, nose and throat swabs, feces, saliva	17.4% 21.6%, 44.8% mild, moderate, severe COVID-19
COVID-19	VeCosCo, Van Berckel (ongoing)	**2022-2023**	125 long covid 75 no long covid	Plasma/serum PET, MRI Cognitive test battery	100% vs 0%
Multiple sclerosis	Amsterdam MS Cohort Huikamp, 2021, Neurology; van Kempen, 2021, JAMA Neurol	**2015** - ongoing	>7,500	Plasma/serum/pbmc, CSF(n~90) fMR, MRI, MEG Cognitive test battery	75%

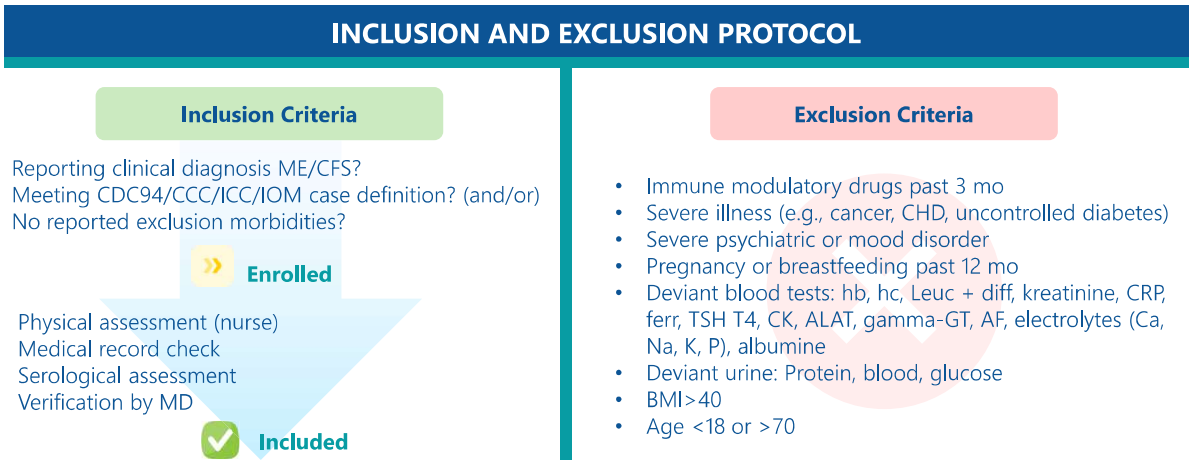

Figure 3. Eligible are patients that meet CDC-94, CCC, ICC or IOM case definitions (either/or), through standardized symptoms assessment (we opted for the DePaul Symptom Questionnaire-2; DSQ-2 [9]). Except for prior diagnosis, the same inclusion and exclusion criteria apply to PIFS patient-control. Exclusion criteria are summarized on the right panel. Exclusion criteria will be obtained from the patient primary physician and supplemented by fresh blood tests. After initial enrollment, final inclusion follows review of clinical data, including physical examination (by nurse) and relevant blood results, by a trained and blinded physician who determines a likely diagnosis.

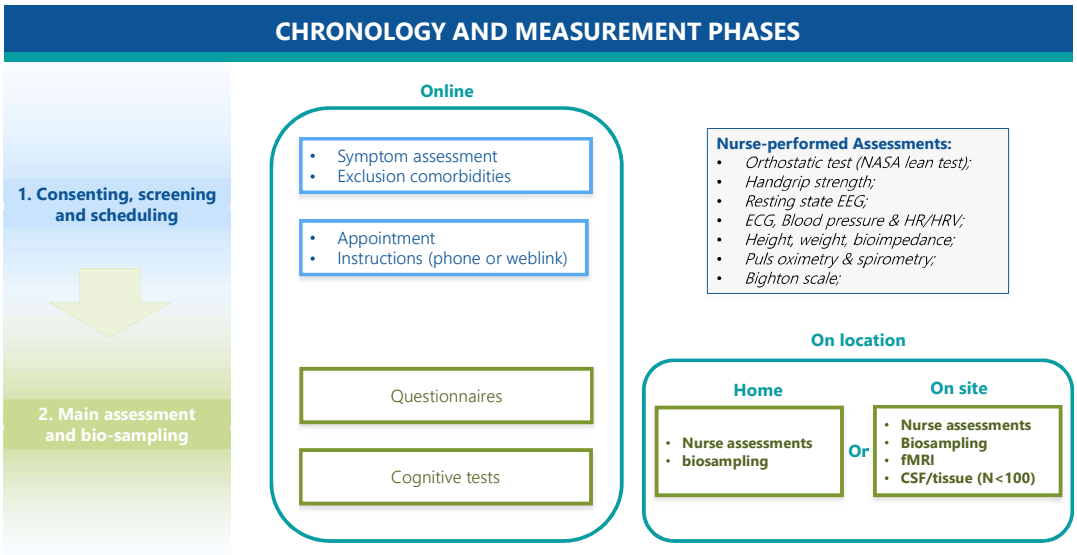

Figure 4. After consenting and enrollment (see **Figure 3**), participants will be contacted to schedule a home or site visit and to be informed about study procedures. Patients, patient-controls, and healthy controls will undergo te same standardized assessment protocols. Questionnaire and cognitive test data will be collected via an on-line portal (in collaboration with Solve M.E.). A trained nurse will perform home-visits to collect biosamples and perform physical assessments. MRI will be collected from a representative subsample (N=350 patients; N=200 HC; N=250 MS/PIFS-controls) on-site. Patients will be reimbursed for travel or offered assisted transport. All patients will be reimbursed for time.