

Trial Nation

Clinical Trials Denmark

CENTER FOR INFECTIOUS DISEASE & IMMUNE MODULATION

A network of Danish infectious disease clinics

Your clinical research partner in infectious
diseases and vaccines

Trial Nation Infectious Disease

The Center for Infectious Disease and Immune Modulation was established in 2016 as a network of Danish hospital clinics specialized in the treatment of infectious diseases and primary immune disorders. The center covers all regions of Denmark and thereby allows **a single point of entry** to a dedicated, national network of hospital departments with a strong focus on clinical research in **infectious diseases, immune modulation, and vaccine trials**.



Over the past 10-15 years, the infectious disease departments in Denmark have built considerable knowledge and expertise in the execution of clinical trials through participation in a wide range of company-sponsored trials but also through an extensive portfolio

of investigator-driven clinical studies. The Center for Infectious Disease and Immune Modulation has experience in both early (phase I and II) as well as late stage (phase III and IV) clinical research. Through a strong research collaboration including all sites the center has established:

- High quality clinical data based on detailed patient registries for diseases such as HIV and hepatitis.
- A solid research infrastructure and collaboration platform across the center enabling expert handling of clinical trials in a national setting.
- An internationally recognized research portfolio in infectious disease and vaccine studies.
- A successful track record for timely delivery of high-quality data from clinical trials.
- Strong capabilities for handling the increasing complexity of clinical research in terms of clinical trial conduct, technological infrastructure, scientific knowledge, and personalized medicine.

The primary objective of the Trial Nation Center for Infectious Disease and Immune Modulation is to offer a single, national platform for clinical research within the therapeutic area. This allows delivery of efficient and high-quality phase I, II, III, and IV trial execution and collaboration with pharmaceutical industry partners.

DANISH UNIVERSITY CLINICS IN TRIAL NATION	REGION
Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet	Capital Region of Denmark
Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre	Capital Region of Denmark
Dept. of Medicine/Infectious Diseases and Clinical Research Unit, Zealand University Hospital, Roskilde	Region Zealand
Department of Infectious Diseases, Odense University Hospital	Region of Southern Denmark
Department of Infectious Diseases, Aalborg University Hospital	North Denmark Region
Department of Infectious Diseases, Aarhus University Hospital	Central Denmark Region

Clinic	Clinical trial phases	Ongoing trials/year		Catchment are	Consultations/year	Contact(s) for trials
		Industry sponsored	Investigator initiated			
Dept. of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet	I, II, III, IV	App. 10	10	n.a.*	>10,000	Professor Jan Gerstoft jan.gerstoft@regionh.dk
Dept. of Infectious Diseases, Copenhagen University Hospital, Hvidovre Hospital	I, II, III, IV	5-10	5-10	1,786,000	20,000	Professor Thomas Benfield thomas.lars.benfield@regionh.dk
Dept. of Medicine/Infectious Diseases and Clinical Research Unit, Zealand University Hospital, Roskilde	II, III, IV	App. 10	App. 10	821,000	TBC	Chief Consultant, PhD, MIH Lothar Wiese low@regionsjaelland.dk
Dept. of Infectious Diseases, Odense University Hospital	II, III, IV	App. 10	>10	1,210,000	10,500	Professor Isik Somuncu Johansen isik.somuncu.johansen@rsyd.dk Project nurse Susan Hansen susan.hansen@rsyd.dk
Dept. of Infectious Diseases, Aalborg University Hospital	II, III, IV	3	3	585,000	>7,000	Professor Henrik Nielsen henrik.nielsen@rn.dk
Dept. of Infectious Diseases, Aarhus University Hospital	I, II, III, IV Incl. FIH	>10	>10	1,292,000	12,000	Professor Lars Østergaard larsoest@rm.dk CTU Manager Nina Breinholt Stærke ninase@rm.dk

*Rigshospitalet is a referral hospital for patients needing highly specialized treatment.

Center services

The Trial Nation Center for Infectious Disease and Immune Modulation handles all requests and trial coordination as one national center. The center has a strong focus on maintaining rapid response times (e.g. time from industry contact to feedback on patient availability). This is supported by access to the established infrastructure and national databases for major disease areas such as HIV, sepsis, pneumonia, and hepatitis (described below). In addition, the clinical partners have access to a broad range of international databases providing companies with a more in-depth evaluation of patient availability from both a national and international perspective. Further, patient-specific treatments, based on genotyping, have been an integrated part of the clinical research in hepatitis C and HIV at all participating clinics. The combined set-up allows an increased focus on personalized therapy supported by centralized laboratory facilities

for genome analyses at Aalborg University Hospital and through the availability of patient material at the Odense University Hospital biobank

Among the services offered by The Trial Nation Center for Infectious Disease are the following:

- One point of entry for all trial queries.
- Rapid turn-around of requests – information on patient availability is based on existing databases.
- Uniform regulatory and ethics approval.
- Uniform contract negotiation for all clinical sites.
- Uniform set of standard operating procedures (SOPs) for all sites.
- A precision medicine approach that includes biobanking and genotyping.
- A full range of complementary services are available aimed specifically at Small and Medium-sized Enterprises (SMEs),

e.g.: assistance with protocol development/scientific content, trial conduct,

sample collection, data collection, report writing, and scientific publication.

Indication	Prevalence (#)	Incidence (#/year)
HIV infection, adults	5.800	185
Chronic Hepatitis C	15.000	180
Chronic Hepatitis B	5.000	250
CNS infections (purulent meningitis)	n.a.	130
Primary Immune Deficiencies (CVID)	300	50
Severe sepsis	n.a.	1.000
Multiresistant infections (obs/isolation)	500	5.000
Cystic fibrosis	400	30
Tuberculosis	275	275
Infectious spondylodiscitis	300	350

Infectious diseases, Prevalence and Incidence in Denmark. The current population of Denmark is app. 5,775,000

Personalized medicine I: Pathogen genotyping and sequencing to individualize treatment

Recent advances in the study of viral infections (e.g. HIV, hepatitis B, and hepatitis C) have underlined the role of genotyping, subtyping and sequencing in predicting clinical response to pharmacological treatment. At the Trial Nation Center for Infectious Disease and Immune Modulation, detailed pathogen analysis allows the introduction of individualized therapy by tailoring antimicrobial chemotherapy to the viral isolate from the patient. This also applies to single nucleotide polymorphisms associated with susceptibility to antiviral compounds.

Aalborg University Hospital has more than 25 years of experience in virology. The first in-

house HCV-PCR was developed in 1990 and the first routine HCV-PCR for quantification was marketed in 1994. More than 20 different virology analyses have been developed in the section for molecular biology diagnostics, some in second or third generation. The laboratory disposes of all molecular diagnostic techniques including several different next-generation sequencing platforms. The laboratory is DANAK accredited according to the ISO 15189 standard, and the laboratory participates in several external quality control networks and international working parties. The laboratory has experience from collaborative projects with industrial partners in developing new analyses and biomarkers.

Personalized medicine II: Biobanks for biomarkers, risk factors, and predictive factors

The heterogeneity in the response to pathogens and to the treatment of infections has increased the focus on personalized medicine within infectious diseases. The heterogeneity

is often not well understood or well characterized but may have important consequences for drug development and drug evaluation in clinical trials. Therefore, research across the

Trial Nation Center for Infectious Disease and Immune Modulation also has a strong focus on the importance of patient characteristics (other than genetics) regarding response to treatment. In the context of personalized medicine, there is focus on the value of biomarkers in assessing risk of disease, choice of therapy, as well as predictive markers of treatment response. The center has estab-

lished large biobanks containing several thousand biological samples (e.g. pneumonia, sepsis, CNS infections, HIV, hepatitis) which may be important tools in the search for biomarkers. Novel biomarkers may further be evaluated in cohort studies and clinical intervention studies and may thus be a way to accelerate drug discovery and development.

DANHIV – A national quality assurance database

The Danish HIV cohort (DANHIV) is a unique national quality assurance database located at Rigshospitalet, Copenhagen. It contains information about all (>7,000) Danish HIV patients diagnosed since 1995, of which 95% will be receiving treatment at the centers included in the Trial Nation Center for Infectious Disease and Immune Modulation. The HIV cohort has been a scientific success as it has formed the basis of more than 100 publications in peer reviewed journals.

In relation to the database, a DNA biobank has also been established. The database is a unique tool to identify potential study candidates as it contains information about co-infection, treatment history, and immunological status. Furthermore, the database can be used in quickly addressing the feasibility of a proposed study. Long term follow-up in patients exposed to investigational agents can also easily be provided.

DANHEP – a nationwide cohort study in hepatitis B and C

Established in 2002, the Danish Database for Hepatitis B and C (DANHEP) is a nationwide open cohort study with ongoing enrolment. DANHEP includes data on people in Denmark who are diagnosed with chronic hepatitis B or chronic hepatitis C virus infection, are >15 years of age, and are receiving follow-up treatment. 17 medical departments specializing in either infectious diseases or gastroenterology at 11 different Danish hospitals participate in the DANHEP collaboration. The cohort includes >7,000 patients with chronic hepatitis C, accounting for approximately half of the estimated number of HCV-infected persons in Denmark. Data includes gender, country of origin, date of inclusion in DANHEP, HCV RNA, HCV genotype, mode of infection, year of infection, last clinical observation, human

immune deficiency (HIV) status, HBsAg status, as well as ALT and alpha-fetoprotein tests. Fibrosis/cirrhosis is estimated by liver elastography (Fibroscan) values and liver biopsy (modified Metavir score). For patients treated for chronic hepatitis C, information on start and end date of treatment, type of treatment, planned duration of treatment, treatment completion, and treatment outcome are registered. One advantage of the current database guidelines is they allow for the identification of patients with specific HCV genotypes with and without fibrosis/cirrhosis who are eligible for antiviral treatment. In Denmark, treatment of chronic hepatitis C is centralized to departments participating in the DANHEP collaboration, therefore most patients treated for chronic hepatitis C will be registered in DANHEP.

Vaccine Studies – a national effort

Vaccination is a simple and cheap intervention to avoid infectious disease-caused morbidity or mortality. Despite vaccination being successful, society faces great opposition toward vaccination (as recently experienced with the surge in measles cases due to lack of vaccination). Measures to actively inform, address, and mitigate the concerns are needed. Over the recent years, Aarhus University Hospital has developed expertise in exploring predictors and determinants for successful vaccination strategies. Aarhus has an established clinical trial unit and has conducted multiple investigator-initiated clinical intervention trials with focus on both prophylactic and therapeutic vaccination. Among other things, the clinical trials have examined the impact of specific tissue types (e.g. HLA-genotypes) on infection outcomes,

response to vaccination and/or adjuvants, as well as immunotherapy. These topics will continue to be explored as part of the ongoing research activities within the center. Further sophisticated molecular immunology analysis ranging from exome sequencing to phenotypic characterization of immune effector cells (e.g. B cells, CD4 T helper cells, Cytotoxic T cells, and Natural Killer cells) are integrated parts of current clinical trials. Moreover, biological pathogen confinement facilities (e.g. BSL3 laboratory) allow translational studies on sample material from patients to infer precision medicine evaluations in a bench-to bedside-to-bench loop. The Trial Nation Center for Infectious Disease and Immune Modulation has experience in vaccine strategies for trials conducted in adults (both healthy and patients) as well as pediatric vaccination trials.

For coordinated request to all clinics, please contact

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Selected publications

- Hallager S, Ladelund S, Christensen PB, Kjær M, Thorup Roegge B, Grønbaek KE et al. Liver-related morbidity and mortality in patients with chronic hepatitis C and cirrhosis with and without sustained virologic response. *Clin Epidemiol*. 2017 Oct 24;9:501-516.
- Hatleberg CI, Prah J, Rasmussen JN, Andersen PH, Bjerrum S, Thomsen VØ et al. A review of paediatric tuberculosis in Denmark: 10-year trend, 2000-2009. *Eur Respir J*. 2014 Mar;43(3):863-71.
- Holden IK, Kehrer M, Andersen AB, Wejse C, Svensson E, Johansen IS. Mycobacterium marinum infections in Denmark from 2004 to 2017: A retrospective study of incidence, patient characteristics, treatment regimens and outcome. *Scientific Reports*. 2018 Dec 1;8(1). 6738.
- INITIO Trial International Co-ordinating Committee, Yeni P, Cooper DA, Aboulker JP, Babiker AG, Carey D et al. Virological and immunological outcomes at 3 years after starting antiretroviral therapy with regimens containing non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or both in INITIO: open-label randomised trial. *Lancet*. 2006 Jul 22;368(9532):287-98.
- Johansen IS, Nielsen SL, Hove M, Kehrer M, Shakar S, Wøyen AV et al. Characteristics and Clinical Outcome of Bone and Joint Tuberculosis From 1994 to 2011: A Retrospective Register-based Study in Denmark. *Clin Infect Dis*. 2015 Aug 15;61(4):554-62.
- Kurth F, Develoux M, Mechain M, Clerinx J, Antinori S, Gjørup IE et al. Intravenous Artesunate Reduces Parasite Clearance Time, Duration of Intensive Care, and Hospital Treatment in Patients With Severe Malaria in Europe: The TropNet Severe Malaria Study. *Clin Infect Dis*. 2015 Nov 1;61(9):1441-4.
- Mocroft A, Laut K, Reiss P, Gatell J, Ormaasen V, Cavassini M et al. Where is the greatest impact of uncontrolled HIV infection on AIDS and non-AIDS events in HIV? *AIDS*. 2018 Jan 14;32(2):205-215.
- Molina JM, Grund B, Gordin F, Williams I, Schechter M, Losso M et al. Which HIV-infected adults with high CD4 T-cell counts benefit most from immediate initiation of antiretroviral therapy? A post-hoc subgroup analysis of the START trial. *Lancet HIV*. 2018 Apr;5(4):e172-e180.
- Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blinded, phase 3, non-inferiority trial. *Lancet HIV*. 2018 May;5(5):e211-e220.
- Nordholm AC, Holm LL, Svensson E, Andersen PH, Johansen IS. Tuberculosis Transmission in Danish Children; A Nationwide Register-Based Study. *Pediatr Infect Dis J*. 2019 Apr;38(4):340-343.
- Ronit A, Gerstoft J, Nielsen L, Mohey R, Wiese L, Kvinesdal B et al. Non-AIDS Comorbidity in People Living with HIV Compared to Uninfected Individuals Ten Years Prior to HIV-Diagnosis. *Clin Infect Dis*. 2018 Sep 28;67(8):1291-1293.
- Ronit A, Kristensen T, Klitbo DM, Gelpi M, Kalhauge A, Benfield T et al. Incidental lung cancers and positive computed tomography images in people living with HIV. *AIDS*. 2017 Sep 10;31(14):1973-1977.
- Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D et al. CD4+ Count-Guided Interruption of Antiretroviral Treatment. *N Engl J Med*. 2006 Nov 30;355(22):2283-96.
- Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallois J, Pol S et al. Efficacy and safety of 8 weeks versus 12 weeks treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet*. 2015 Mar 21;385(9973):1087-97.
- Zurek Munk-Madsen M, Toft L, Kube T, Richter R, Ostergaard L, Søgaard OS et al. Cellular immunogenicity of human papillomavirus vaccines Cervarix and Gardasil in adults with HIV infection. *Hum Vaccin Immunother*. 2018 Apr 3;14(4):909-916.
- Østergaard L, Vesikari T, Absalon J, Beeslaar J, Ward BJ, Senders S et al. A Bivalent Meningococcal B Vaccine in Adolescents and Young Adults. *The New England Journal of Medicine*. 2017 Dec 14;377(24):2349-2362.

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