3e programmabiljeenkomst
Personalised Medicine
20 juni 2019
Utrecht

Managing Director
Drs. Astrid Schut
a.schut@wcn.life

13:40 uur
Start parralelle sessies

Sessie A
Hoe zet je een multi-center studie op en hoe hou je de vaart erin?
• Tips voor een vlotte start en verloop van een project.
  Dr. Wim-Jan Kool, director business development Lygature
• Drs. Astrid Schut, managing director Werkgroep Cardiologische Centra Nederland (WCN)
ZonMW 20 juni 2019

• WCN en de LoDoCo2
• Contracten en andere vertragende factoren
• Gezamenlijk doel versus andere belangen
  • Competitie andere trials
  • Gebruik bestaande expertise
• Motivatie onderzoekers – hou de vaart erin
Randomisaties
Binnen 2 jaar

> 3580 Randomisaties
Binnen 2 jaar

150.1
Rate (monthly). Expected due date nov 2018

<table>
<thead>
<tr>
<th>V2</th>
<th>Six months</th>
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<tbody>
<tr>
<td>Continuation after open label run-in:</td>
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<tr>
<td>Yes</td>
<td>3609</td>
</tr>
<tr>
<td>No, Intolerant</td>
<td>259</td>
</tr>
<tr>
<td>No, choice patient</td>
<td>144</td>
</tr>
<tr>
<td>No, choice doctor</td>
<td>59</td>
</tr>
<tr>
<td>&lt;NA&gt;</td>
<td>14</td>
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<tr>
<td>Total</td>
<td>4085</td>
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WCN

Physicians Network for Cardiovascular Research in the Netherlands
Deliver high quality clinical research to improve our patients’ health

Through partnership with pharmaceutical industry leaders, CRO’s and non-profit research institutes from trial design to publication.
Committed to deliver high quality clinical research to improve our patients’ health

We are

600 investigators
> 6 million patients

> 50 hospitals

One network
A brief overview

- Founded in 1988
- Recruited >30,000 participants in 15+ years of clinical research
- >50 cardiology hospitals
- ~45 active studies
- Industry sponsored and investigator initiated studies
- 4-5 board members
Our focus

WCN as partner to sponsor

WCN as NLO

WCN as sponsor

Unburden the PI

Patent focus

Service to sponsors

Randomised clinical trials

Industry initiated

Investigator driven

Service to sponsors
About our organization

» Driven and executed by physicians - network members

» Elected board and dedicated office staff

» Membership means dedication to quality and targets

» Network culture focus on collaboration and commitments
Governance

Elected Board

Office staff
Our services

Feasibility assessment
- Internal survey
- Site selection committee
- Site list input based on network expertise and metrics

Site activation
- Experts on local regulations
- Centralized contract management
- EC and RA applications

National Lead Office
- Full trial services
- Site monitoring
- Project management

Scientific services
- Protocol design
- Steering committee memberships
Feasibility assessment
» Selection committee assesses interest, performance and study portfolio
» Site list input based on network expertise and metrics

Communications
» Online platform for research professionals
» Annual congress with focused Investigator Meetings
» Member meetings, brainstorm meetings for Study Directors

Recruitment and retention
» Patient recruitment and retention support
» Setting realistic targets based on track record

Site activation
» Centralized contract negotiations and payment management
» Support or guidance in local processes

How we operate

Our principles

WCN Study Director
» Dedicated investigator for each trial
» Leading by example

How we operate
Enrolment strategy and tools

Recruitment oversight
on website & mobile app

Screening strategy
supported by CTcue search tool

Accountability
for achieving the agreed targets

Various tools
- e-mail, newsletters, investigator calls,
- Research Professional forum

Study director
active involvement to support recruitment

Monthly reporting
and follow-up with site staff
Our mobile website

DAPA-HFrEF
- Inclusies
- Documenten
- RP Posts

DAPA-HFrEF (Follow-up)
Inclusies WCN vs. Inclusies wereldwijd
- Totaal WCN: 85
- Totaal wereldwijd: 4764

Inclusies WCN (toename per maand)

Ranglijst deelnemende centra
1. Jeroen Bosch Ziekenhuis (23)
2. Máxima Medisch Centrum (18)
3. ORA Research and Genetics (11)
4. Franciscus Gasthuis (11)
5. Girod (3)

DAPA-HFrEF: RP Posts
- Screening lijsten ingevuld voor vergoeding?
  Janneke Ios, WCN
- Lichamelijk onderzoek op werkbladen
  Petra van Boe-Penning, Research
  verpleegkundige, derde wetenschappelijke
  vakgroep kaste Ziekenhuis
- DAPA / WCN / juni was een goede maand?
  Leonie Vroock, WCN
- Leerlijst DAPA patiënten... tips?
  Suzanne Jansen, Research verpleegkundige
  Gez. Ziekenhuizen
- DAPA-HF / WCN / statusupdate
  Leonie Vroock, WCN
- DAPA-HF / WCN / 1e patiënt
  gerandomiseerd door Snewek
  Leonie Vroock, WCN
Commitment to science

» International scientific network
» Pharma and ARO leadership network
» Input in trial protocol design
» National leads with strong publications and relationships
» IT-guided input in feasibility (CTcue)
<table>
<thead>
<tr>
<th>Investigator responsibilities</th>
<th>Sponsor company responsibilities</th>
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<tbody>
<tr>
<td>Investigator’s Qualifications and Agreements</td>
<td>Quality Management</td>
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<tr>
<td>Adequate Resources</td>
<td>Quality Assurance and Quality Control</td>
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<tr>
<td>Medical Care of Trial Subjects</td>
<td>Contract Research Organization (CRO)</td>
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<tr>
<td>Communication with IRB/IEC</td>
<td>Medical Experts</td>
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<tr>
<td>Compliance with Protocol</td>
<td>Trial Design</td>
</tr>
<tr>
<td>Investigational Product(s)</td>
<td>Trial Management, Data Handling, and Record Keeping</td>
</tr>
<tr>
<td>Randomization Procedures and Unblinding</td>
<td>Investigator Selection</td>
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<tr>
<td>Informed consent of Trial Subjects</td>
<td>Allocation of Responsibilities</td>
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<tr>
<td>Records and Reports</td>
<td>Compensation to Subjects and Investigators</td>
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<tr>
<td>Safety Reporting</td>
<td>Financing</td>
</tr>
<tr>
<td>Premature Termination or Suspension of a Trial</td>
<td>Notification/Submission to Regulatory Authority</td>
</tr>
<tr>
<td>Final reports</td>
<td>Confirmation of Review by IRB/IEC</td>
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<tr>
<td></td>
<td>Information on Investigational Product(s)</td>
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<tr>
<td></td>
<td>Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)</td>
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<td></td>
<td>Supplying and Handling Investigational Product(s)</td>
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<tr>
<td></td>
<td>Record Access</td>
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<tr>
<td></td>
<td>Safety Information</td>
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<tr>
<td></td>
<td>Adverse Drug Reaction Reporting</td>
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<tr>
<td></td>
<td>Monitoring (Purpose, selection and qualifications of monitors, extent and nature of monitoring, monitor’s responsibilities, monitoring procedures, monitoring report)</td>
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<tr>
<td></td>
<td>Audit (Purpose, selection and qualification of auditors, auditing procedures)</td>
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<tr>
<td></td>
<td>Noncompliance</td>
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<tr>
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<td>Premature Termination or Suspension of a Trial</td>
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<tr>
<td></td>
<td>Clinical Trial/Study Reports</td>
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<tr>
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<td>Multicentre Trials</td>
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</table>
Perform our own RCT...

• The idea: WCN Pitch
• Funding: Our first grant – ZonMW GGG/ HS
  Public Private Collaboration
• Drug: Pharma consortium
• Investigators: Cornel & Mosterd
  “Match making” - Eikelboom
  Nidorf & Thompson
• Team: WCN staff and network monitors
• Sites: WCN network in kind contribution
• Patients: 3608 in 2 jaar in 30 sites
You don't know what you don't know.

~ Socrates

Information is not knowledge. The only source of knowledge is experience. You need experience to gain wisdom.

~ Albert Einstein
The Low Dose Colchicine (LoDoCo) trials

“In the confident hope of a miracle”

Arend Mosterd
Jan Hein Cornel
Mark Nidorf
Peter Thompson

Dit project wordt mogelijk gemaakt door:
Prevention of (recurrence of) CV disease
The cardiology consultation
Coronary Artery Disease
Prevention of CV disease
Residual risk

Fourier / Evolocumab, Sabatine M. NEJM 2017
Prevention of CV disease
Inflammation and Crystallopathies
occlusion leading to infarction
Colchicum autumnale
Colchicine

1. Crocus like species

2. Over 2000 years in use for gout treatment

3. Anti inflammatory effect

4. Affordable

**DRUG REDISCOVERY**
Gloriosa Superba
Human uses

The alkaloid-rich plant has long been used as a traditional medicine in many cultures. It has been used in the treatment of:

- gout
- infertility
- open wounds
- snakebite
- ulcer
- arthritis
- cholera
- colic
- kidney problems
- typhus
- itching
- leprosy
- bruises
- sprains
- hemorrhoids
- cancer
- impotence
- Nocturnal emission
- smallpox
- sexually transmitted diseases
- many types of internal parasites
- anthelmintic
- used as a laxative
- used as an alexiteric
- the sap is used to treat acne and head lice
- it may cause abortion
- in parts of India, extracts of the rhizome are applied topically during childbirth to reduce labor pain.
Gout
Gout in the vessel wall?
Cholesterol crystal induced arterial inflammation
Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf, MD, MBBS,* John W. Eikelboom, MBBS,† Charley A. Budgeon, BSc (Hons),‡ Peter L. Thompson, MD§
Perth, Australia; and Hamilton, Ontario, Canada

Objectives
The objective of this study was to determine whether colchicine 0.5 mg/day can lower events in patients with clinically stable coronary disease.

Background
The presence of activated neutrophils in culprit atherosclerotic plaques of patients raises the possibility that inhibition of neutrophil function with colchicine reduces instability and thereby improves clinical outcomes in patients with stable coronary artery disease.

Methods
In a clinical trial with a prospective, randomized, observer-blinded endpoint design, 282 patients with acute coronary syndrome, out-of-hospital cardiac arrest, or noncardiovascular mortality were assigned to aspirin and/or clopidogrel (93%) and statins (95%) and then assigned to either 0.5 mg/day of colchicine or placebo for a median of 3 years. The primary endpoint was death or nonfatal myocardial infarction. The primary endpoint occurred in 15 of 282 patients (5.3%) who received colchicine (10.0%) assigned no colchicine (hazard ratio: 0.33; 95% confidence interval [CI] 0.08–0.80). The median time to death or nonfatal myocardial infarction in the colchicine group was 21 days longer than in the noncolchicine group. In a prespecified secondary on-treatment analysis, the group assigned to colchicine who withdrew within 30 days due to intestinal intolerance had an HR of 0.33 (95% CI 0.18–0.59; P = 0.001).

Figure 2
Freedom from the Primary Outcome

Freedom from the primary outcome (acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) by treatment. CI = confidence interval; HR = hazard ratio.
LOW-DOSE COLCHICINE FOR SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

5.552 Patients with stable coronary artery disease to detect 30% reduction in MACE + (CV death, MI, stroke, revasc) in 3 years
New Holland – Australia

LoDoCo2
Partners in Drug Repurposing
LoDoCo2 – The Netherlands

Potential: an affordable drug for many (25M/ year - RIVM) and prime example of drug repurposing

• How to proceed to a label? CBG/ ZIN/ VWS
• Implementation Patients & Prescribers
Mark Nidorf: When Clinicians take their Ideas from Bench to Bedside it Requires a Leap of Faith

... they need to go forward aware of uncertainties but

“In the confident hope of a miracle”

* Admiral Martin de Bertendona, Commander of the [Spanish Armada] Levant squadron Expressing doubts about the chances of success of the invasion of England
Lesons learned are many...

- WCN – sponsor role in LoDoCo2
- Contracting and other delay
- Manage: protocol, charters (DSMB, EAC), scientific and regulatory governance
- Collaboration= people: find common goal and be honest about your agenda
- Align processes between 2 continents
- Merge separate different data sets
- Competition other funded trials – lucky shot & power of the network
- Use existing expertise – partners, staff, network monitors, ZonMW/ HS support
- Motivate investigators – network culture, commitment
- Risk Based Trial Management versus Inspection Readiness (NVZA Veldnorm)
Alleen ga je sneller, maar samen kom je verder