RETrospective observational Study to assess the clinical management and outcomes of hospitalised patients with Complicated Urinary tract INfection in countries with high prevalence of multidrug resistant Gram-negative bacteria

RESCUING
(COMBACTE-MAGNET WP5)

AMSTERDAM , NEDERLAND | APRIL 2016

Miquel Pujol, MD

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RESCUING - Partners

- **Academic Leaders:**
  - Leader: Miquel Pujol (Bellvitge University Hospital, Spain)
  - Co-Leader: Leonard Leibovici (Tel-Aviv University, Israel)

- **EFPIA* Leaders:**
  - Leader: Irith Wiegand (AiCuris, Germany)
  - Co-Leader: Ibironke Addy (AiCuris, Germany)

- **Other Partners:**
  - North Bristol NHS Trust, UK
  - University College London, UK
  - University Medical Center Utrecht, NL/ CLIN-NET

(*) EFPIA: European Federation of Pharmaceutical Industries and associations

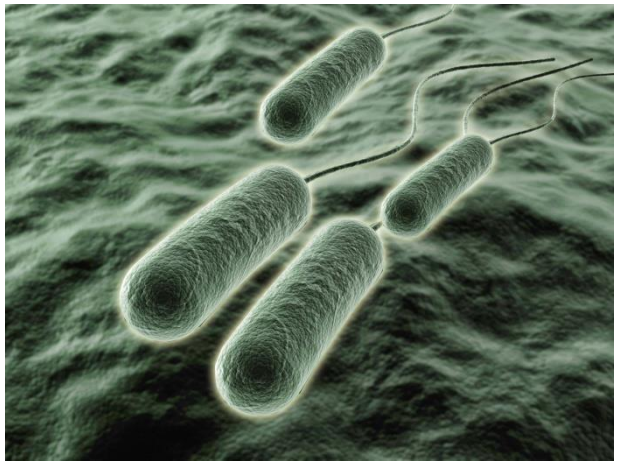
Rationale

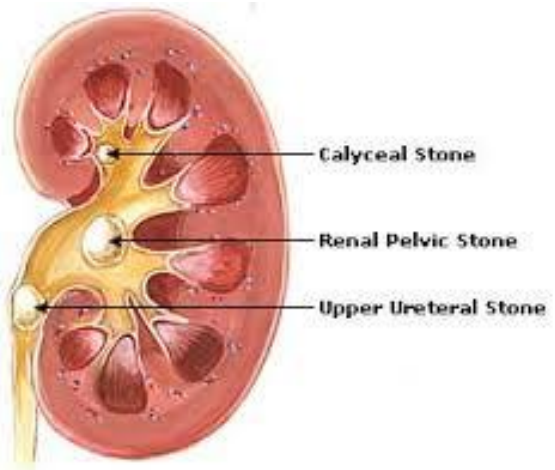
- **Increasing prevalence of MDR-GNB** (multi-drug resistant Gram-negative bacteria) worldwide is a major concern
- cUTI frequent among **hospital/health-care related infections**
- Gather and provide **current data from European regions with a high prevalence of MDR GNB** regarding:
  - **Clinical management** and **outcomes of hospitalised** patients with cUTI
  - **Modifiable risk factors** for adverse outcomes
  - Impact of **inappropriate empirical therapy**
  - **Costs** of cUTI

Complicated Urinary Tract Infection (cUTI)

Complicated urinary tract infection occurs in individuals **with functional or structural abnormalities of the genitourinary tract**, including pyelonephritis

FDA 2015.cUTI: Developing Drugs for Treatment Guidance for Industry





RESCUING
Primary Objective

To determine the **outcome of hospitalised patients with complicated urinary tract infections** (cUTI) and **identify the risk factors associated with treatment failure** in this cohort of patients

Rescuing Secondary Objectives

- To identify **clinical characteristics** and demographic factors of hospitalised patients with cUTI
- To identify the **main causative multidrug resistant gram negative bacteria** (MDR GNB) and their most frequent resistance profiles
- To define **risk factors associated with cUTI caused by MDR** GNB.
- To describe **clinical management data** of hospitalised patients with cUTI
- To determine the **modifiable risk factors** associated with early treatment failure in patients with cUTI
- To determine **length of hospital stay** in patients with cUTI
- To determine **duration of antibiotic therapy** in patients with cUTI
- To determine **mortality rate** of hospitalised patients with cUTI
- To estimate **the cost per case of cUTI** measured by length of hospital stay, Intensive Care Unit requirements, medications, tests and need for urological intervention and haemodialysis
- To estimate the **total national cost** of illness due to cUTI in participating countries
- To **help identify patient types and potential clinical trial sites** for future clinical trials in cUTI

Secondary Objectives
Epidemiological-Clinical Issues

To identify:

- **Clinical characteristics** and **demographic factors** of hospitalised patients with cUTI
- **Main causative multidrug resistant gram negative bacteria** (MDR GNB) and their most frequent resistance profiles
- **Risk factors associated with cUTI caused by MDR** GNB.
- **Modifiable risk factors** associated with **early treatment failure** in patients with cUTI

To describe

- **Clinical management data** of hospitalised patients with cUTI

Secondary Objectives
Outcome and Costs

To determine:

- **Length of hospital stay** in patients with cUTI
- **Mortality rate** of hospitalised patients with cUTI
- **The cost per case of cUTI** measured by length of hospital stay, ICU requirements, medications, tests and need for urological intervention and haemodialysis
- **Total national cost** of illness due to cUTI in participating countries

To **help:**

- **Identify patient types and potential clinical trial sites** for future clinical trials in cUTI

Study Design

- Multinational, Multicentre, Retrospective, Observational, Cohort study
- Countries: Bulgaria, Greece, Hungary, Israel, Italy, Romania, Spain & Turkey
- Twenty-one sites in eight countries
- Recruitment target:1000 patients (40-50 cases per site)
- Hospitalised patients from January 2013 to December 2014
- Diagnosis of cUTI as the primary cause of hospitalisation and patients hospitalised for another reason but who developed cUTI during their hospitalisation.
- Patients will be identified by searching for ICD-9 CM or ICD-10 CM codes at discharge on the hospital administration system

Selected Countries

- Spain
- Italy
- Hungary
- Romania
- Bulgaria
- Greece
- Turkey
- Israel

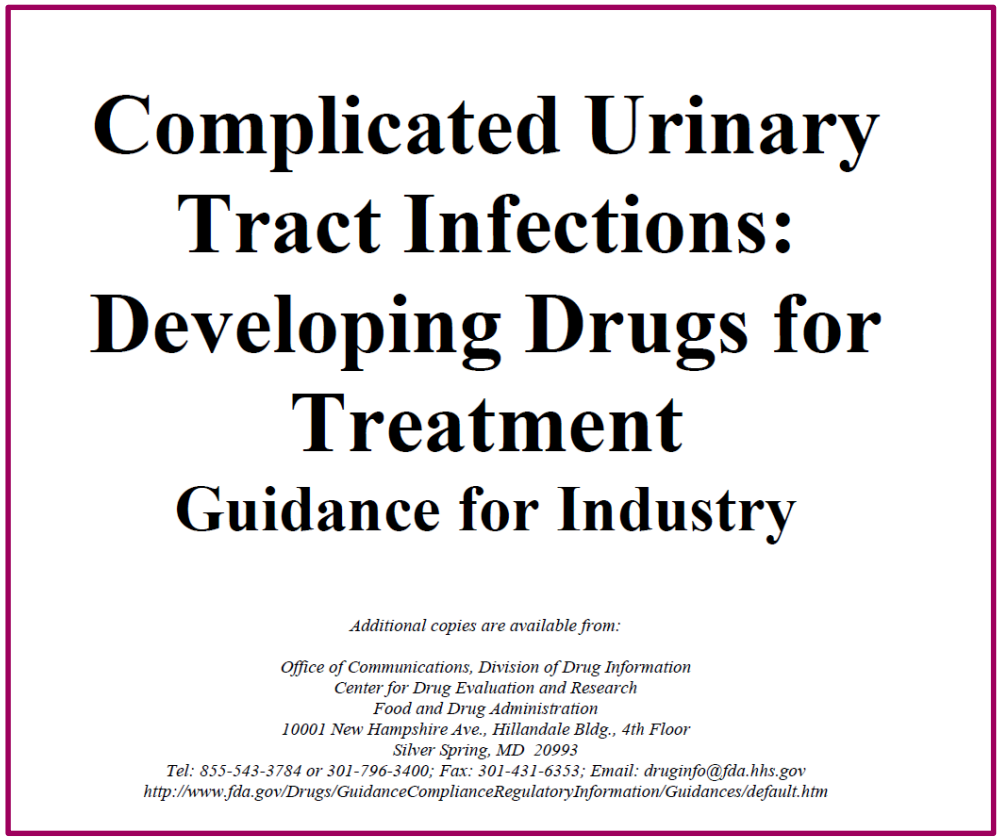
Main Inclusion Criteria

Hospitalised patient + cUTI

- Related to indwelling urinary catheterisation
- Related to pyelonephritis with normal tract anatomy
- Related to anatomical urinary tract modification
- Related to obstructive uropathy
- Related to other events

Primary Study Endpoint

Primary Endpoint: **treatment failure**



Complicated Urinary Tract Infections: Developing Drugs for Treatment

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993
Tel: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

FDA 2015

Treatment failure

Presence of any of the following conditions:

- **Signs or symptoms of cUTI** present at diagnosis that have **not improved by days 5 to 7** of appropriate antibiotic therapy
- **New cUTI** related symptoms that have developed **within 30 days** of the original cUTI diagnosis
- **Urine culture taken within 30 days** of the original cUTI diagnosis, either during or after completion of therapy, that grows greater than or equal to 10^4 CFU/mL of the original pathogen identified in the diagnostic sample
- **Death irrespective of cause** within 30 days of the original cUTI diagnosis

Secondary Study Endpoints

The following secondary end-points will be evaluated:

- Time to clinical response, in days
- Time to urological intervention for source control, in days
- Duration of antibiotic therapy, in days
- Length of hospital stay, in days
- Time to death, in days
- Hospital mortality
- All cause mortality within 30 days of the original cUTI diagnosis
- All cause of mortality for two months after hospital discharge
- Cost per case of cUTI
- Readmissions to the hospital within 60 days of hospital discharge
- Adverse events related to antibiotic treatment including: moderate or severe allergic reactions, severe renal impairment, *Clostridium difficile* infection.

Secondary Study Endpoints (I)

Clinical:

- Time to clinical response, (days)
- Time to urological intervention for source control (days)
- Time to death (days)
- Duration of antibiotic therapy (days)
- Length of hospital stay (days)

Secondary Study Endpoints (II)

Outcomes:

- Hospital mortality
- All cause mortality within 30 days of the original cUTI diagnosis
- All cause of mortality for two months after hospital discharge

Costs:

- Cost per case of cUTI
- Readmissions to the hospital within 60 days of hospital discharge

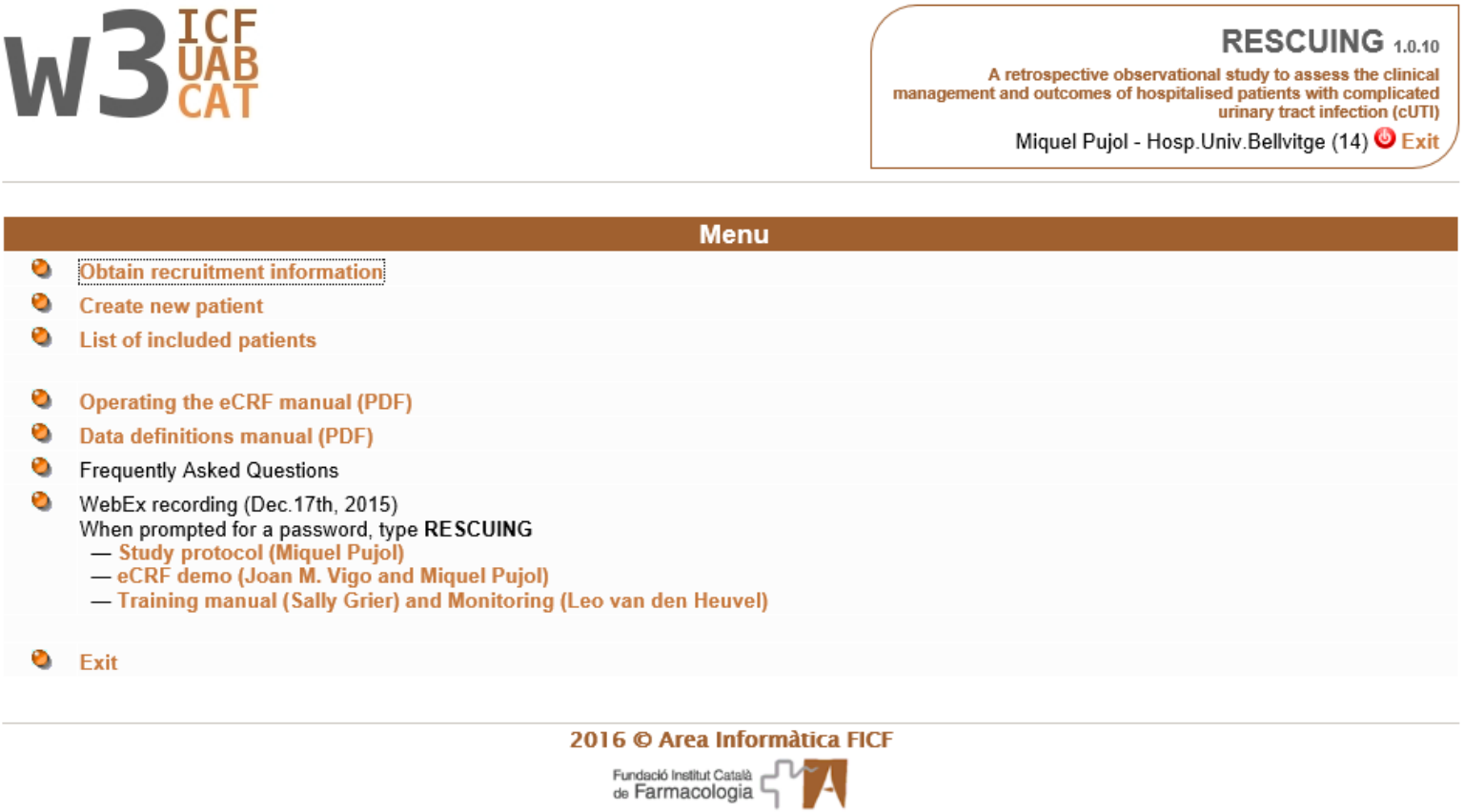
Adverse events related to antibiotics:

- Moderate or severe allergic reactions
- Severe renal impairment
- *Clostridium difficile* infection

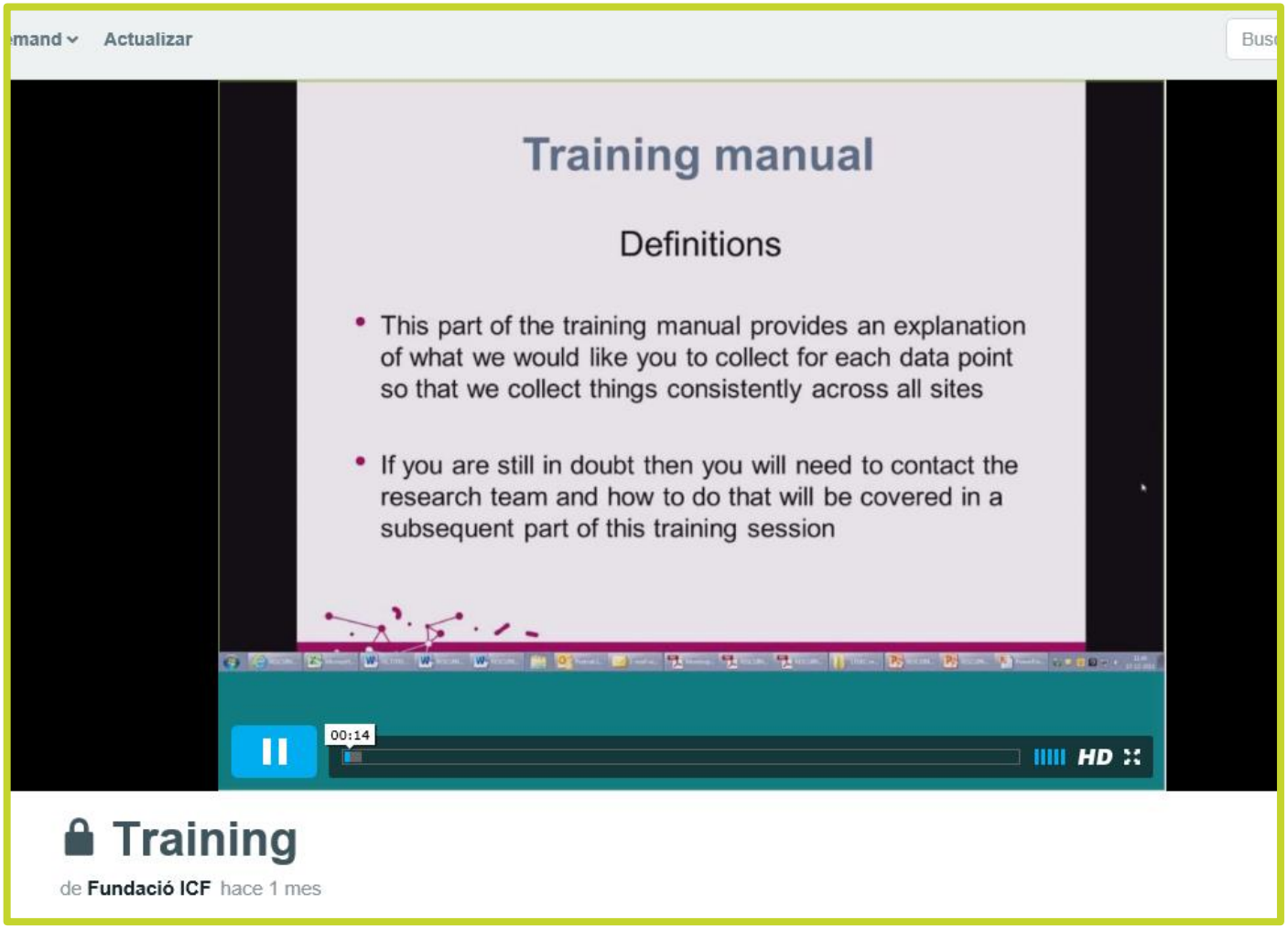
Data Collection

- Data will be collected retrospectively
- Hospitalised patients from January 2013 to December 2014
- Data items will be collected from patient notes, electronic patient records, the hospital patient administration system and the hospital laboratory systems
- Data will be recorded into the web-based study electronic Case Report Form (eCRF)
- For all patients a standardised set of information will be recorded in the eCRF including; Demographics, Co-morbidities including those required to calculate a modified Charlson score, Functional capacity, Place of acquisition of infection, Predisposing risk factors, Clinical data, Clinical pathology data, Microbiological data, Imaging test data, Infection management, Antibiotic therapy, Outcomes, Details of discharge and readmission
- The follow up period will be for up to two months after discharge from the admitting hospital

Web-based Study Electronic Case Report Form (eCRF)



Videos Site initiation via WebEx



WP5 Update - Key Objectives for 2015

Study letters to sites/researchers with questionnaire	✓
Site selection process (Site selection plan, meetings and selection)	✓
Finalize study protocol	✓
Finalize study tools: eCRF, trial database, training and monitoring manuals	✓
Investigator/site initiation meetings	✓
Achieve ethics/regulatory approval in first target country	✓
Data collection commencement	✓

WP5 Update

- Activities and goals in the next period to move these 2015 objectives forward (Jan – May 2016)
  - Complete site documentation/contracts
  - Achieve ethics/regulatory approval and monitoring at all sites
  - Completion of patient datasets

- Learnings/insights since the inception of the consortium
  - Regular TCs with open communication and joint efforts, have continued to improve output
  - To achieve a joint goal on time, emphasis on clear responsibilities shared within the team

ISSUE 3

April 2016

MONTHLY NEWSLETTER

RESCUING

Study Highlights

- 271 cases are entered into eCRF
- 18 sites in 8 countries started data entry
- 10 monitor visits have been performed

We are pleased to send you the third issue of the RESCUING newsletter that will provide you with study status updates, reminders and helpful tips.

Contact Details:

Monitoring coordinator

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eCRF account

Joan Miquel Vigo

jmv@icf.uab.cat

ECCMID 9-12th April 2016

COMBACTE will be represented in the exposition hall, booth number 37A. Please visit the booth if you have any questions related to the RESCUING study or COMBACTE in general.

We really appreciate your hard work in progressing enrollment. Thank you for your continued dedication to the RESCUING study!

The RESCUING Team

Clinical Topics

- **Definition inclusion criteria "hospitalized":** The act of being hospitalized for a period of stay >24 hours in a medical/surgical or critical ward of a hospital. Admission at the emergency care unit > 1 day under observation is not considered hospitalization.
- **Additional cases:** Currently we have asked every site to enrol 40 cases. However, to obtain our target of 1000 cases, we will need to approach several sites to enrol additional cases. Would it be feasible for your site to include additional cases? Please let us know by replying to the following email: n.cuperus@umcutrecht.nl.

Enrollment Status

Country	Number of sites	Number of cases started	Number of cases completed
Spain	3	62	51
Greece	2	44	39
Bulgaria	2	19	16
Romania	3	16	13
Turkey	2	54	18
Hungary	1	18	6
Israel	3	42	37
Italy	2	16	13
Total	**18**	**271**	**193**

Monitoring topics

- **How to answer an eCRF query?** When you are in the relevant form, you need to click on the red icon besides the Query heading. A popup will then open. Please type an answer to the query, then click 'Save' to update the query. Finally you must exit the form without saving it again by clicking on the "Exit without saving" button.
- **Why does the query icon remain red after answering it?** Whenever you save the form, the system automatically checks for problems it has been programmed to recognise and will flag them as red. To avoid this happening when you have answered a query and clicked save to update the query, you then need to exit the form by clicking on the "Exit without saving" button. This will change the icon to brown to show the query has been answered.
- We are still aiming to complete data collection and entry into the eCRF of 1000 cases by **30th April 2016**. This will be subject to review on an ongoing basis by the study team.

Timelines

- First Hospital Ethical Committee approval already achieved
- First inclusion of cases: December 2015
- Final inclusion of cases: April-May 2016
- Statistical analysis: June 2016
- Results report: September 2016
- First draft version manuscript: October – November 2016

Clinical Trial registration

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Study to Assess Management and Outcomes of Hospitalised Patients With Complicated UTI (RESCUING) (RESCUING)

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2016 by Institut d'Investigació Biomèdica de Bellvitge

Sponsor:
Institut d'Investigació Biomèdica de Bellvitge

Collaborators:
Tel Aviv University
AiCuris Anti-infective Cures GmbH
University of Bristol
UMC Utrecht

Information provided by (Responsible Party):
Miquel Pujol, Institut d'Investigació Biomèdica de Bellvitge

ClinicalTrials.gov Identifier:
NCT02641015

First received: December 23, 2015
Last updated: January 7, 2016
Last verified: January 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

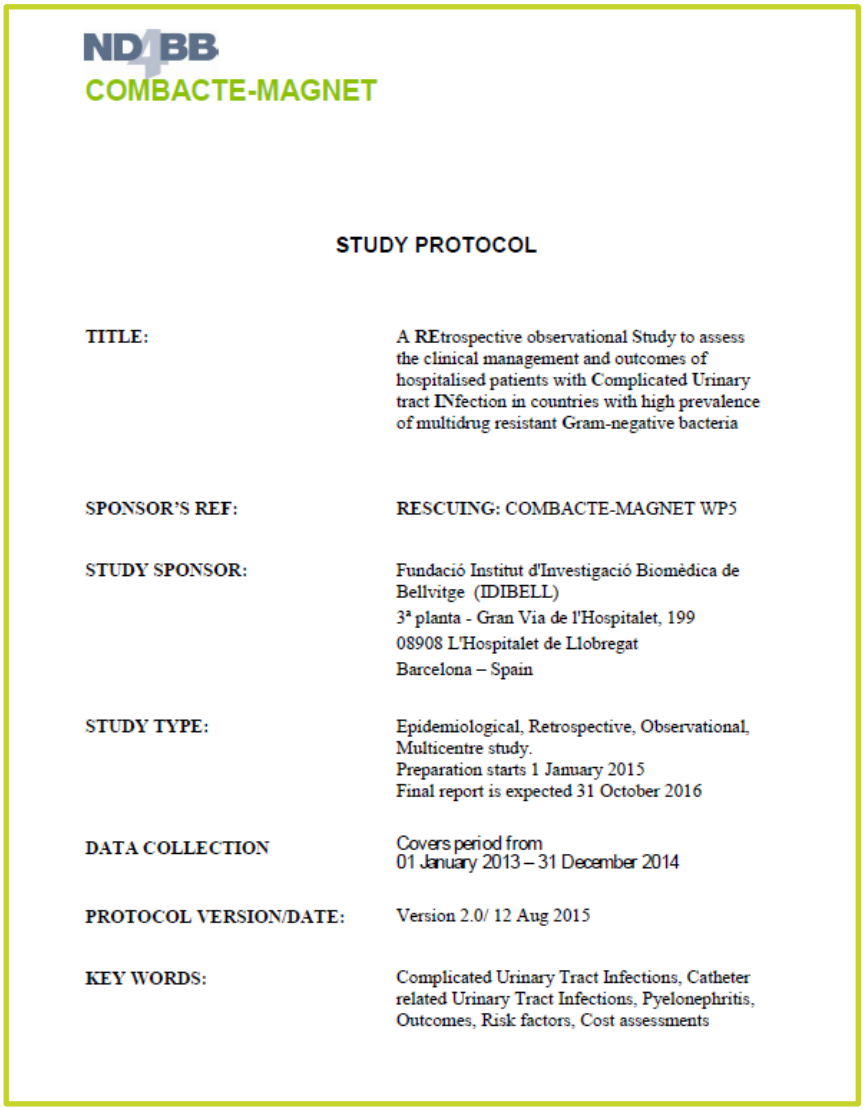
Purpose

A retrospective observational study to assess the clinical management and outcomes of hospitalised patients with complicated urinary tract infection in countries with high preva

Condition

Urinary Tract Infections
Bacterial Resistance

Study Protocol: British Medical Journal Open Submitted for publication February 2016



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COMBACTE-MAGNET

STUDY PROTOCOL

TITLE:	A REtrospective observational Study to assess the clinical management and outcomes of hospitalised patients with Complicated Urinary tract INfection in countries with high prevalence of multidrug resistant Gram-negative bacteria
SPONSOR'S REF:	RESCUING: COMBACTE-MAGNET WP5
STUDY SPONSOR:	Fundació Institut d'Investigació Biomèdica de Bellvitge (IDIBELL) 3ª planta - Gran Via de l'Hospitalet, 199 08908 L'Hospitalet de Llobregat Barcelona – Spain
STUDY TYPE:	Epidemiological, Retrospective, Observational, Multicentre study. Preparation starts 1 January 2015 Final report is expected 31 October 2016
DATA COLLECTION	Covers period from 01 January 2013 – 31 December 2014
PROTOCOL VERSION/DATE:	Version 2.0/ 12 Aug 2015
KEY WORDS:	Complicated Urinary Tract Infections, Catheter related Urinary Tract Infections, Pyelonephritis, Outcomes, Risk factors, Cost assessments

WP5 conclusions

- We have completed the proposed milestones for 2015
- The study is ongoing and 18 of 21 centres have begun the inclusion of cases.
- Three centres have not started due to delays in the approval of the ethics committee or the approval of contracts.
- It is anticipated that these problems will be resolved this month, and by the end of May all cases will be included.