SEPARATING THE WHEAT FROM THE CHAFF IN CLINICIAN-INDUSTRY RELATIONS

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SEPARATING THE WHEAT FROM THE CHAFF IN CLINICIAN-INDUSTRY RELATIONS

- Define situations leading to better patient care
- Outline the challenges of building clinical research from scratch and keeping it going
- Find situations where academia, industry and patient care align synergistically

My disclosures: Actelion steering committee for Cadazolid and investigator, Advisory panel Rebiotix, Davoterra, Pfizer

Canadian Medical Association principles in industry-sponsored studies

- Ethically defensible, social responsible, scientifically valid
- Ethics oversight
- Protection of privacy
- Trials registry
- Monetary transparency
- Incremental costs covered by sponsor
- Funding disclosure on publication
- Authorship only if substantive contribution
- No agreement to limit right of MD to disclose information
- Avoid marketing or promotion for industry
- Ethical oversight of studies
- CME = education to improve care
- Biase against satellite symposia
- CME content decided by MD organizers to ensure scientific validity, objectivity, completeness
- Disclosure of conflict of interest
- Avoid links between funding and products
- Unrestricted grants for edu
- Reasonable, transparent and disclosed financial cost for physician involvement

Differential needs of clinicians and the pharmaceutical industry

- Advancing patient care- the patient is sole focus
- Best practice evidence-based medicine
- Cost-effective prescribing
- ID/MM identification of care issues in need of better solutions
- Platform for evaluation

Clinical care in hospital and community setting

- Advancing patient care
- Support use/sales of products marketed [edu materials, samples, edu support]
- Utilize health care systems to support industry objectives of therapeutic pipeline development

Pharmaceutical industry

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Pharmaceutical industry

Barriers to the conduct of infectious diseases clinical trials (1)

- Infections are time sensitive; time to interception for recruitment is short
- Clinician cannot be on 24/7 call and available to intercept events
- In most instances single center studies do not recruit sufficient numbers of subjects
- Multi-center studies run the risk of involvement without recognition, trial objectives may not fit with patient need
- PI has to be willing to be accountable for costs incurred. Divisions and departments can take on this responsibility, but this is not common. = private business model.

Barriers to the conduct of infectious diseases clinical trials (2)

- In Canada, academic positions usually do not come with research support [annual operating grant, tech salaries, laboratory]
- New agents needing evaluation have been fewer
- Clinical trial capability within medical staff declines, inertia is difficult to overcome
- It is a business where external funds are brought in to pay for work done plus pay overhead to hospital/university.

Targeting infections of interest

- CAP, HAP/VAP, cUTI, cIAS, cABSSSI, anti-viral trials Hepatitis, HIV, CMV, antifungal, CDI, pathogen focused trials eg Antibiotic-resistant GNB
- Vaccine studies: population identification not always easy, recruitment is more controlled, but the follow up for efficacy evaluation can be laborious

Building from the ground up

To pay for start up for clinical research and to ensure a viable operation, these are the tasks:

- Identify common infections which have quality outcomes issues
- Patient access available, directly or indirectly
- Feasible, practical protocol is registered with IRB
- Budget to account for expected # patients, overhead, expenses, cash cushion.
- Study team [difficult to be solo]: ID services, training program, general medical and surgical services, ER, outpatients [some you will have to pay off]
- Finding the right clinical support staff: admin, trial coordinator, for recruitment, follow up, data handling

Building from the ground up (2)

To pay for start up for clinical research and to ensure a viable operation, these are the tasks:

- Over time, PI, sub I, co-investigators and ID/MM service change / evolve as an expert group
- PI and co-investigators become the local and regional expert for clinical care
- Farm the whole population of patients and physicians for an indication by taking referrals of patients who have target indications, CME feed back to MDs
- We need the cooperation of laboratory / microbiologists, IPC, pharmacy, our colleagues to be successful; all help acknowledged

Rewards...absolutely essential

- Organizing RCTs is labor intensive such that recruitment of small numbers of cases is not rewarding financially or academically.
- A large subject detection and capture system eg city-or -region wide increase the viability of a trial organization and is itself a reward.
- Financial remuneration beyond expenses is generally not permitted and is a conflict of interest issue. However, monies left over can go into residual accounts for self -initiated projects, student projects, division/department.
- Authorship citations for yourself, your division/department/university

More rewards

- Networking with other investigators nationally, internationally over time brings increased recognition.
- Departments and faculties need to assign academic credits for the conduct of RCTs/ clinical investigation
- State of the art treatments even in an RCT setting improves patient care
- Local studies complement industry trials, sub-studies, or spin offs.
- Industry income into universities complements or adds to tricouncil and public funding.
- On the need to manage without being too much of a burden, financially and lifestyle. Needs large /case reimbursement to account for overhead and study costs. Industry tries to pay on a per task budget spreadsheet. The budget should take into account down time, salary increases, unforeseen costs i.e. a cushion is needed. Importance of laying the groundwork to make a clinical trial work, before the trial starts.

Staying out of financial trouble

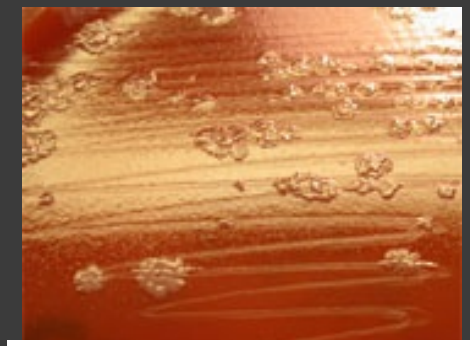
There is a need to manage without being too much of a burden, financially and avoid negative lifestyles.

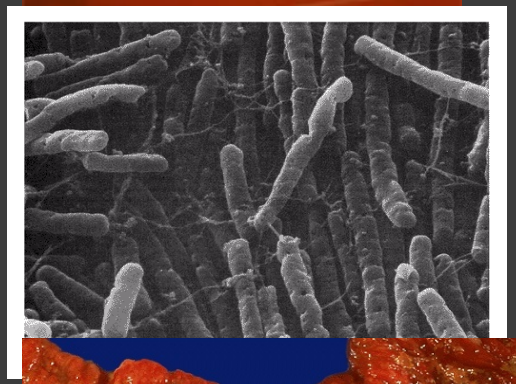
Needs large /case reimbursement to account for overhead and study costs. Industry tries to pay on a per task budget spreadsheet. The budget should take into account down time, salary increases, unforeseen costs i.e. a cushion is needed.

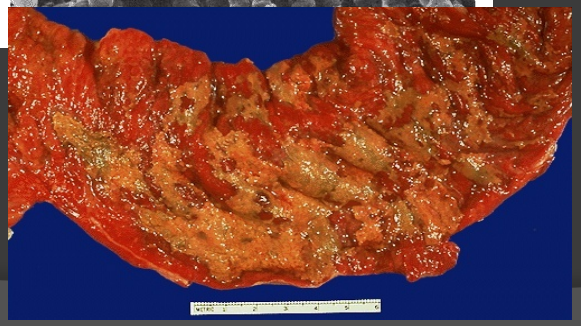
Importance of laying the groundwork to make a clinical trial work, before the trial starts.

Clostridium difficile: bad bug #2.

Health care facility fecal -oral spread; Hospitals as hyperendemic foci
Low level presence of spores in community setting, food/environmental sources







- **spore former, in food/meats, soil, dwellings. One World* epidemiology**
- **In feces of 3-14% of admitted patients**
- **Antibiotics kill normal bacteria, high *C. difficile* counts/toxin → colitis and death**
- **~500,000 cases/y, 29,000 deaths/30d (2011)* USA with 4.8 Billion $ excess hospital costs/year**; 38,000 cases /year in Canada (2012)*****
- **4.1 cases/10,000 pt-days (2008) Eurosurveillance 2016**
- **~1/2 to 2/3 cases are nosocomial**

Riley TW 2012* , CDC Feb. 25 2015**; Levy A OFID 2015 ***.

Clinical trials on *C. difficile* in Calgary 2002-present. Why it works

- 1998 regional model for IPC and formation of CLS
- All hospital cases rates of *C. difficile* and also community outreach
- Daily screening, one sentence line in CLS reports on availability of studies,
- Wide open call to 'team'
- Support with IPC UofC labs including Snyder Infection Immunity and Inflammation institute.
- Western Canada microbiome initiative

- Tolevamer phase 2 2002-2004 (vs vancomycin)
- Fidaxomicin phase 2 2004-5, ascending dose
- Tolevamer (vs metro or vanco) 2006-8
- Fidaxomicin phase 3, 2 trials (2nd with Mike Parkins) 2008-10
- Medarex (bezlotoxumab) 2010
- Surotomycin (CB 183,315) phase 2 2010-11
- Actelion phase 2, asc dose vs vanco 2011-12
- Surotomycin phase 3 2013-4
- Actelion phase 3 2014-2017
- FMT Alberta Health 2014-2017

How cdi clinical research works in Calgary.

- Population-based epidemiology model, as is the rest of the province. Region-wide Infection Prev. & Control is notified on all new positive tests for C.difficile [GDH + proceed to PCR], hospital/ER and community cases
- IPC search hospital info sys for profiles, apparent 1^{o} or first recurrent, go to ward to ask primary team to ask if ok to review for RCT;
- For outpatients, a fax is sent to the primary care team informing of RCT available and short synopsis.
- Lab output also has a one sentence note that treatment trials may be available an call numbers for study coordinator and PI
- If primary care MD is interested in treatment esp. if patients are recurrent, intolerant of metronidazole, failed metronidazole, cannot pay for other agents, they can contact study team to discuss case. If symptoms/signs support active disease, patients are seen ASAP, max. within 24 h. or at patient's availability.

CDI model continued

- QCC C.difficile Quik Chek complete as point of care testing for trial entry
- Routine collection of fecal samples for microbiome and pathogen dynamics
- Send out of samples via local laboratory to central laboratory for the studies
- Electronic data capture on study website
- Contract research organization oversight of cases and QC checks by sponsor.

Characteristics for successful conduct of RCTs that would advance patient care.

- Properties, preclinical data supporting a benefit greater than available with standard
- Randomized DB, controlled trial, registered, sample size for at least Non-inferiority
- Patients have a direct benefit from being in study
- Trial staff make a commitment to also account for continued treatment post trial to resolve the problem before sending the patient back to primary care
- Sufficient volume contribution such that academic credits are available to the PI/sub I
- Or alternate financial benefits to sub I's.
- Finances are not in deficit
- Sustained program over time
- Sub-studies and spin off studies, conducted during the conduct of the main trial creates opportunities for both the trial staff and the sponsor.

Characteristics of a strong ID/Med Micro division/cluster

- Excellence in patient care is the focus.
- Where care also meshes with industry objectives, synergies in care and knowledge translation research
- Non-clinical staff cannot lead in this area
- ID/MM staff can be completely competent in carrying out this task, but generally, MM do not reach out to carry out bedside and clinic follow up on the scale required for clinical trials.
- Academic medicine has a purpose to provide UG and post-grad education, and CME for practitioners, but also should seek proficiency in generating new data to achieve better care locally and externally.
- Basic sciences, translational clinical research is not mutually exclusive
- Canadian Universities are not well funded to perform this function, such that Pis need to be opportunitists recognizing what conditions need to be met to be successful
- The department heads need to recognize and reward such work.

Questions?