

# Hayashi's Problem

Tom Jefferson

Cochrane ARI group

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Hello I am Tom Jefferson. This is what my friends say of my work: "it is mind boggling that medical journals that publish Dr. Jefferson's work do not question his provocative analyses"

# Cochrane review on Neuraminidase Inhibitors (NIs), 1999, 2006, 2008, 2009.....

www.thelancet.com Published online January 19, 2006 DOI: 10.1016/S0140-6736(06)67970-1

Articles

## Antivirals for influenza in healthy adults: systematic review



T Jefferson, V Demicheli, D Rivetti, M Jones, C Di Pietrantonj, A Rivetti

for zanamivir; 1.30, 1.13–1.50 for oseltamivir provided medication was started within 48 h of symptom onset. Viral nasal titres were significantly diminished by both drugs (weighted mean difference  $-0.62$ ,  $-0.82$  to  $-0.41$ ). Oseltamivir at 150 mg daily was effective in preventing lower respiratory tract complications in influenza cases (OR 0.32, 0.18–0.57). We could find no credible data on the effects of oseltamivir on avian influenza.

# Kaiser et al.

(Archives of Internal Medicine 2003)

## ORIGINAL INVESTIGATION

### Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations

Laurent Kaiser, MD; Cynthia Wat, MBBS, MRCP; Tracy Mills, MSc; Paul Mahoney, MSc; Penelope Ward, MBBS; Frederick Hayden, MD

**Background:** Influenza causes lower respiratory tract complications (LRTCs), particularly bronchitis and pneumonia, in both otherwise healthy adults and those with underlying conditions. The aim of this study was to assess the effect of oseltamivir treatment on the incidence of LRTCs leading to antibiotic treatment and hospitalizations following influenza illness.

**Methods:** We analyzed prospectively collected data on LRTCs and antibiotic use from 3564 subjects (age range, 13-97 years) with influenzalike illness enrolled in 10 placebo-controlled, double-blind trials of oseltamivir treatment.

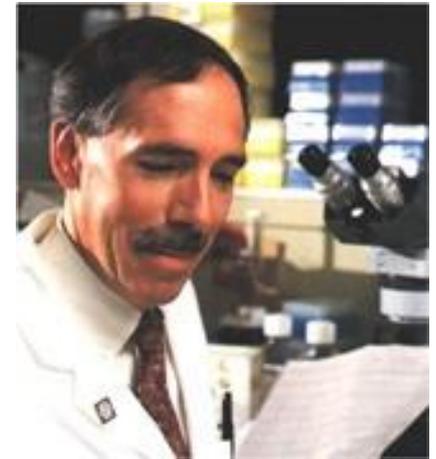
**Results:** In adults and adolescents with a proven influenza illness, oseltamivir treatment reduced overall antibiotic use for any reason by 26.7% (14.0% vs 19.1% with placebo;  $P < .001$ ) and the incidence of influenza-related LRTCs resulting in antibiotic therapy by 55% (4.6% vs

10.3% with placebo;  $P < .001$ ). In those subjects considered at increased risk of complications, 74 (18.5%) of 401 placebo recipients developed an LRTC leading to antibiotic use compared with 45 (12.2%) of 368 oseltamivir recipients (34.0% reduction;  $P = .02$ ). Hospitalization for any cause occurred in 18 (1.7%) of 1063 placebo recipients compared with 9 (0.7%) of 1350 oseltamivir-treated patients (59% reduction;  $P = .02$ ). In contrast, among subjects with an influenzalike illness but without a confirmed influenza infection, the incidence of LRTCs (6.7% vs 5.3%), overall antibiotic use (19.7% vs 19.3%), or hospitalizations (1.7% vs 1.9%) was similar between placebo and oseltamivir recipients, respectively.

**Conclusion:** Oseltamivir treatment of influenza illness reduces LRTCs, antibiotic use, and hospitalization in both healthy and "at-risk" adults.

*Arch Intern Med.* 2003;163:1667-1672

# Profs Laurent Kaiser & Fred Hayden



# Kaiser 2003

“Our analysis found ... oseltamivir significantly reduced influenza-related LRTCs, associated antibiotic use, and the risk of hospitalization. This effect was observed in both at-risk subjects and otherwise healthy individuals.”

Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003;163:1667-72.

- Manufacturer funded meta-analysis
- Included 10 manufacturer funded RCTs from the late 1990s
  - 2/10 published (1397 pts)
  - 8/10 never published (2691 pts)

For  
HHS  
CDC  
EMA  
Aus TGA  
Roche.com  
Cochrane 2006  
Reason  
Kaiser 2003

Against  
FDA  
Japan PMDA  
Tamiflu.com  
Cochrane 2009  
Reason  
unproven claim



# Professor John Treanor

Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA. 2000 Feb 23;283(8):1016-1024.

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**ORIGINAL CONTRIBUTION**

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## Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza A Randomized Controlled Trial

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John J. Treanor, MD

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Frederick G. Hayden, MD

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Peter S. Vrooman, MD

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Rick Barbarash, PharmD

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Robert Bettis, MD

**Context** Previous studies have shown oseltamivir, a neuraminidase inhibitor, to be effective in preventing influenza and treating experimental influenza.

**Objective** To evaluate the efficacy and safety of oseltamivir in the treatment of naturally acquired influenza infection.

**Design** Randomized, placebo-controlled, double-blind study conducted January through March 1998.

# Professor Karl Nicholson



THE LANCET • Vol 355 • May 27, 2000

ARTICLES

## Articles

### **Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial**

*K G Nicholson, F Y Aoki, A D M E Osterhaus, S Trottier, O Carewicz, C H Mercier, A Rode, N Kinnersley, P Ward, on behalf of the Neuraminidase Inhibitor Flu Treatment Investigator Group\**

**Summary**

**Introduction**

# Professor John Treanor



## ABSTRACTS OF THE IDSA 38th ANNUAL MEETING

### 611 Reduction in the Symptoms and Complications of Influenza A and B in Patients Treated with Oseltamivir (the Time-to-Treatment Study Group)

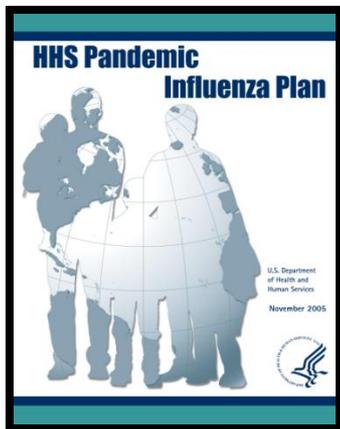
JOHN J TREANOR, Univ of Rochester, Rochester, NY

Oseltamivir is an oral inhibitor of the neuraminidase enzyme of influenza A and B viruses with significant virologic and clinical efficacy in man. Oseltamivir was studied in a multicenter, placebo-controlled, double-blind, symptom-duration-stratified study. Subjects who met a case definition of influenza consisting of fever  $\geq 100^{\circ}\text{F}$  with at least one respiratory (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches/pains, fatigue, headache and chills/sweats) were randomized 2:1 to 75mg oseltamivir (O) or placebo (P) po bid for 5 days. 1459 patients were enrolled at 164 US study sites. The patient population ranged in age from 13 to 80 years, 16% were vaccinated and over 50% had underlying medical conditions (6% with COPD/asthma). A total of 1063 (73%) had laboratory documented influenza infection; 81% had influenza A; 19% had influenza B. The presence of cough and fever were independent predictors of influenza infection. The median duration of illness, defined as the time to alleviation of all 7 major flu symptoms, was 120.5 hrs in influenza-infected P recipients and 96.3 hrs in O recipients ( $p < 0.0001$ ). The median duration of each of the individual symptoms included in the symptom scores was also decreased by oseltamivir, as follows: chills/sweats (34% reduction), cough (31%), fatigue (33%), headache (29%), myalgia (24%), nasal congestion (42%), sore throat (20%), and fever (33%). Severity of illness, as measured by the area under the curve of symptom scores, was reduced by treatment (P=1049 score.hours, O=837 score.hours, median difference 203, 95% CI 117-289). Lower respiratory tract complications reduced with O included bronchitis (P 4%, O 2%) and pneumonia (P 2%, O 0.3%). The results of this study are very ~ to those reported in a phase III trial conducted in the U.S. (38<sup>th</sup> ICAAC, 1998) and demonstrate a consistent beneficial effect of early antiviral treatment of influenza with oseltamivir in populations including adolescents, the elderly and others with co-morbid conditions.

# HHS Pandemic Influenza Plan (2005)

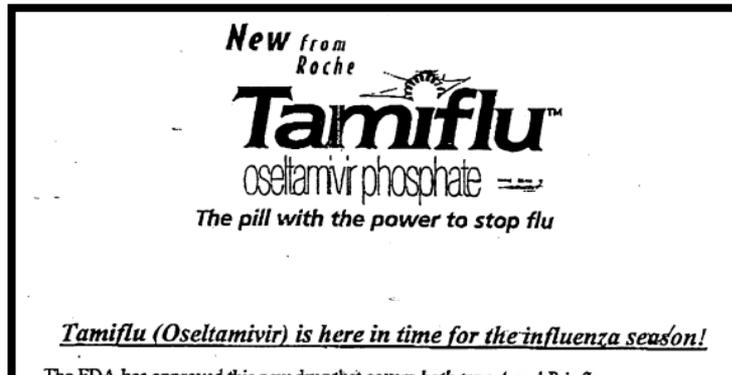
(courtesy of Peter Doshi)

- HHS: “Critical assumptions. Treatment with a neuraminidase inhibitor (oseltamivir [Tamiflu®] or zanamivir [Relenza®]) will be effective in **decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for interpandemic influenza), and will also decrease mortality.**” (p.D-20)
- HHS: “There are **no data** on the effectiveness of neuraminidase inhibitors in preventing either serious morbidity (e.g., requirement for intensive care) or mortality (see July 2005 recommendations of the AHIC [ACIP?] ....” (p.S7-12)
- ACIP 2005: “One study assessing oseltamivir treatment primarily among adults reported a reduction in complications, necessitating antibiotic therapy compared with placebo [**Kaiser 2003**].”



# Tamiflu promotional materials

(courtesy of Peter Doshi)



“Serious bacterial infections may begin with influenza-like symptoms or may co-exist with or occur as complications during the course of influenza. **Tamiflu has not been shown to prevent such complications.**”

Tamiflu.com  
October 25, 2010

April 14, 2000 – FDA warning letter to Roche

## Misleading Efficacy Claims

In the homemade pieces, Roche has presented the following misleading efficacy claims:

*“The pill with the power to stop the flu,”*

*“Tame-the-flu with Tamiflu,”*

*“Tamiflu will reduce duration of the flu by 31%,”*

*“Tamiflu will reduce the severity of influenza symptoms by 38%,”* and

*“Tamiflu reduces incidence of secondary complications (i.e. bacterial infections) by 45%.”*

These claims are misleading because they suggest greater efficacy for Tamiflu than has been demonstrated by substantial evidence. For example, you have used the phrases “power to stop the flu” and “Tame-the-flu” and presented study results in percentages that overstate the 1.3-day difference in flu symptom improvement with Tamiflu compared with placebo. Further, you have claimed reductions in severity and incidence of secondary infections with Tamiflu that are misleading because they are not supported by substantial evidence.

“Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. **TAMIFLU has not been shown to prevent such complications.**” — Tamiflu label

# CDC promotional materials (2010)

(courtesy of Peter Doshi)

The Centers for Disease Control and Prevention (CDC) urges you to take the following steps to protect yourself and others from influenza (the flu).

## CDC SAYS: "TAKE 3" ACTIONS TO FIGHT THE FLU

CDC URGES YOU TO TAKE 3 ACTIONS TO PROTECT AGAINST THE FLU.

### #1 Vaccinate

- CDC recommends a yearly flu vaccine as the first and most important step in protecting against flu viruses.
- While there are many different flu viruses, the flu vaccine protects against the three viruses that research suggests will be most common.
- The 2010-2011 flu vaccine will protect against an influenza A H1N1 virus, an influenza B virus and the 2009 H1N1 virus that caused so much illness last season.
- Everyone 6 months of age and older should get vaccinated against the flu as soon as the 2010-2011 season's vaccine is available.
- People at high risk of serious flu complications include young children, pregnant women, people with chronic health conditions like asthma, diabetes or heart and lung disease and people 65 years and older.
- Vaccination of high risk persons is especially important to decrease their risk of severe flu illness.
- Vaccination is also important for health-care workers, and other people who live with or care for high risk people to keep from spreading flu to high risk people.
- Children younger than 6 months are at high risk of serious flu illness, but are too young to be vaccinated. People who care for them should be vaccinated instead.

### #2 Stop Germs

- Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it.
- Wash your hands often with soap and water. If soap and water are not available, use an alcohol-based hand rub.
- Avoid touching your eyes, nose and mouth. Germs spread this way.
- Try to avoid close contact with sick people.
- If you are sick with flu-like illness, CDC recommends that you stay home for at least 24 hours after your fever is gone except to get medical care or for other necessities. (Your fever should be gone without the use of a fever-reducing medicine.)
- While sick, limit contact with others as much as possible to keep from infecting them.

### #3 Antiviral Drugs

- If you get the flu, antiviral drugs can treat your illness.
- Antiviral drugs are different from antibiotics. They are prescription medicines (pills, liquid or an injection) and are not available over-the-counter.
- Antiviral drugs can make illness milder and shorten the time you are sick. They may also prevent serious flu complications.
- It's very important that antiviral drugs be used early (within the first 2 days of symptoms) to treat people who are very sick (such as those who are hospitalized) or people who are sick with flu symptoms and who are at increased risk of severe flu illness, such as pregnant women, young children, people 65 and older and people with certain chronic health conditions.
- Flu-like symptoms include fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills, and fatigue. Some people may also have vomiting and diarrhea. People may be infected with the flu, and have respiratory symptoms without a fever.

**FLU-LIKE SYMPTOMS INCLUDE:**

fever	cough	sore throat	runny or stuffy nose
body aches	headache	chills	fatigue

Some people may also have vomiting and diarrhea. People may be infected with the flu, and have respiratory symptoms without a fever.

 U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

For more information, visit [HTTP://WWW.FLU.GOV](http://www.flu.gov) or call 800.CDC.INFO

Page 2 of 2

“Antiviral drugs can make illness milder and shorten the time you are sick. **They may also prevent serious flu complications.**”

[http://www.cdc.gov/flu/pdf/freeresources/general/take3\\_poster\\_print.pdf](http://www.cdc.gov/flu/pdf/freeresources/general/take3_poster_print.pdf)

# Dr Keiji Hayashi

(courtesy of Swiss TV)



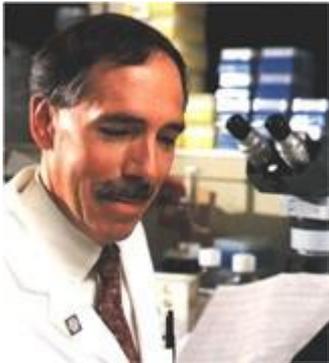
Comment posted 14 July 2009

We have some questions on the conclusion in your Oseltamivir review especially about the prevention of complication. You described that “Oseltamivir 150 mg daily prevented lower respiratory tract complications (OR 0.32, 95% CI 0.18 to 0.57).” (in abstract). However, we have found that this conclusion is based on the other review (Kaiser2003) and not on your own data analysis. The authors of the review were four employees of F. Hoffman-La Roche Ltd, one paid consultant to F. Hoffman-La Roche Ltd and Kaiser. We cannot find any raw data about this conclusion from your review. Kaiser’s review included 10 RCTs; two RCTs (Nicholson 2000 and Treanor 2003) were published as articles in the peer-reviewed medical journal (JAMA and Lancet), but other 8 RCTs were proceedings of congress (5 RCTs), abstracts of the congress (one RCT) and meeting (one RCT) and data on file, Hoffmann-La Roche, Inc, Nutley, NJ (one RCT). The lower respiratory tract complication rates of these articles were summarized on table: there was no significant difference between Oseltamivir and placebo, and their Odds Ratio’s (ORs) were 1.81. But ORs of other 8 RCTs were 4.37. We strongly suppose that the reviewer’s conclusion about the complications was mainly determined by these 8 RCTs, we should appraise the 8 trials rigidly. Without this process it’s difficult to conclude that oseltamivir can prevent lower respiratory tract complications

# Profs Laurent Kaiser & Fred Hayden



“I suggest to contact Roche directly to get access to the files”. Email from Kaiser 17 August 2009



“ I have searched but cannot find the original files related to this 2003 publication. Before and again after my 2+ years at WHO in Geneva, I was obliged to move offices at the University several times and downsize. The files appear to have been discarded. My co-author Laurent Kaiser, now professor at the University of Geneva, is copied on this reply, as he may have his own sources. The questions posed by the inquirer are not clear to me, but if original data or unpublished study reports are required, they will likely need to come from Roche, the sponsor of these studies”. Email from Hayden 14 August 2009



# Professor John Treanor

ABSTRACTS OF THE IDSA 38th ANNUAL MEETING

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“...[Treanor] told the *BMJ* that as far as he could remember, the trial published in *JAMA* was the only large study of oseltamivir he had ever participated in. ...Channel 4 News put it to Roche that Professor Treanor said that he didn’t actually participate in study M76001 and doesn’t remember presenting it a meeting in 2000. Dr David Reddy, Roche’s Global Pandemic Taskforce leader, said: “It’s not infrequent that you may have somebody who authors but they don’t actually present it at a conference, it depends upon their availability.” (D Cohen, *BMJ* 2009)

## 611 Reduction in the Symptoms and Complications of Influenza A and B in Patients Treated with Oseltamivir (the Time-to-Treatment Study Group)

JOHN J TREANOR, Univ of Rochester, Rochester, NY

Oseltamivir is an oral inhibitor of the neuraminidase enzyme of influenza A and B viruses with significant virologic and clinical efficacy in man. Oseltamivir was studied in a multicenter, placebo-controlled, double-blind, symptom-duration-stratified study. Subjects who met a case definition of influenza consisting of fever  $\geq 100^{\circ}\text{F}$  with at least one respiratory (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches/pains, fatigue, headache and chills/sweats) were randomized 2:1 to 75mg oseltamivir (O) or placebo (P) po bid for 5 days. 1459 patients were enrolled at 164 US study sites. The patient population ranged in age from 13 to 80 years, 16% were vaccinated and over 50% had underlying medical conditions (6% with COPD/asthma). A total of 1063 (73%) had laboratory documented influenza infection; 81% had influenza A; 19% had influenza B. The presence of cough and fever were independent predictors of influenza infection. The median duration of illness, defined as the time to alleviation of all 7 major flu symptoms, was 120.5 hrs in influenza-infected P recipients and 96.3 hrs in O recipients ( $p < 0.0001$ ). The median duration of each of the individual symptoms included in the symptom scores was also decreased by oseltamivir, as follows: chills/sweats (34% reduction), cough (31%), fatigue (33%), headache (29%), myalgia (24%), nasal congestion (42%), sore throat (20%), and fever (33%). Severity of illness, as measured by the area under the curve of symptom scores, was reduced by treatment (P=1049 score.hours, O=837 score.hours, median difference 203, 95% CI 117-289). Lower respiratory tract complications reduced with O included bronchitis (P 4%, O 2%) and pneumonia (P 2%, O 0.3%). The results of this study are very ~ to those reported in a phase III trial conducted in the U.S. (38<sup>th</sup> ICAAC, 1998) and demonstrate a consistent beneficial effect of early antiviral treatment of influenza with oseltamivir in populations including adolescents, the elderly and others with co-morbid conditions.

# Professor Karl Nicholson



When asked a similar question, Nicholson said he did not recall seeing the primary data. He said that the statistical analysis had been conducted by Roche and he analysed the summary data. “While Roche has admitted that “medical writers were used to draft some of the above papers” and Nicholson said that Roche did employ a medical writer to draft the manuscript, they both argued that at the time of submission—before the 2003 Good Publication Practice Guidelines, produced with the help of the drug industry and recently updated 20 —it was standard practice for unnamed medical writers to be used”. (Cohen, BMJ 2009)

ARTICLES

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## Articles

### **Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial**

*K G Nicholson, F Y Aoki, A D M E Osterhaus, S Trottier, O Carewicz, C H Mercier, A Rode, N Kinnersley, P Ward, on behalf of the Neuraminidase Inhibitor Flu Treatment Investigator Group\**

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Summary

Introduction



“I did not perform an independent analysis of the primary data, which was not required or requested by *JAMA at the time of submission*, and I do not have access to the primary data, which I also never requested.” (Treanor quoted in Cohen, BMJ 2009)



“When asked a similar question, Nicholson said he did not recall seeing the primary data. He said that the statistical analysis had been conducted by Roche and he analysed the summary data”. (Cohen, BMJ 2009)

# Unanswered questions

- How many trials are there?
- Who is responsible for each trial?
- Why were large phase III trials (e.g. M76001, NAIA 3002) not published?
- Who is responsible for the decision not to publish studies in which humans were randomised?
- What are the harms and benefits of NIs?
- Why are trials been published 10 years after completion?
- Are the Clinical Study Reports (CSRs) a reliable source of evidence?
- Are we going to get the full CSRs?
- How can regulatory approval be based on selected trials instead of totality of evidence?
- Is the body of NI pharmaceutical evidence reliable?
- Why do we have divergent indications across regulators (TF)?

# New methods



# New Methods

- Identify all trials (trial programme) **Agree**
- Identify and retrieve all CSRs and regulatory material **Agree**
- TOCE **Agree**
- Weave evidence of trial programmes together **Disagree**
- Assess it – if reliable analyse **What does reliable mean? Complete? Trustworthy? Both?**





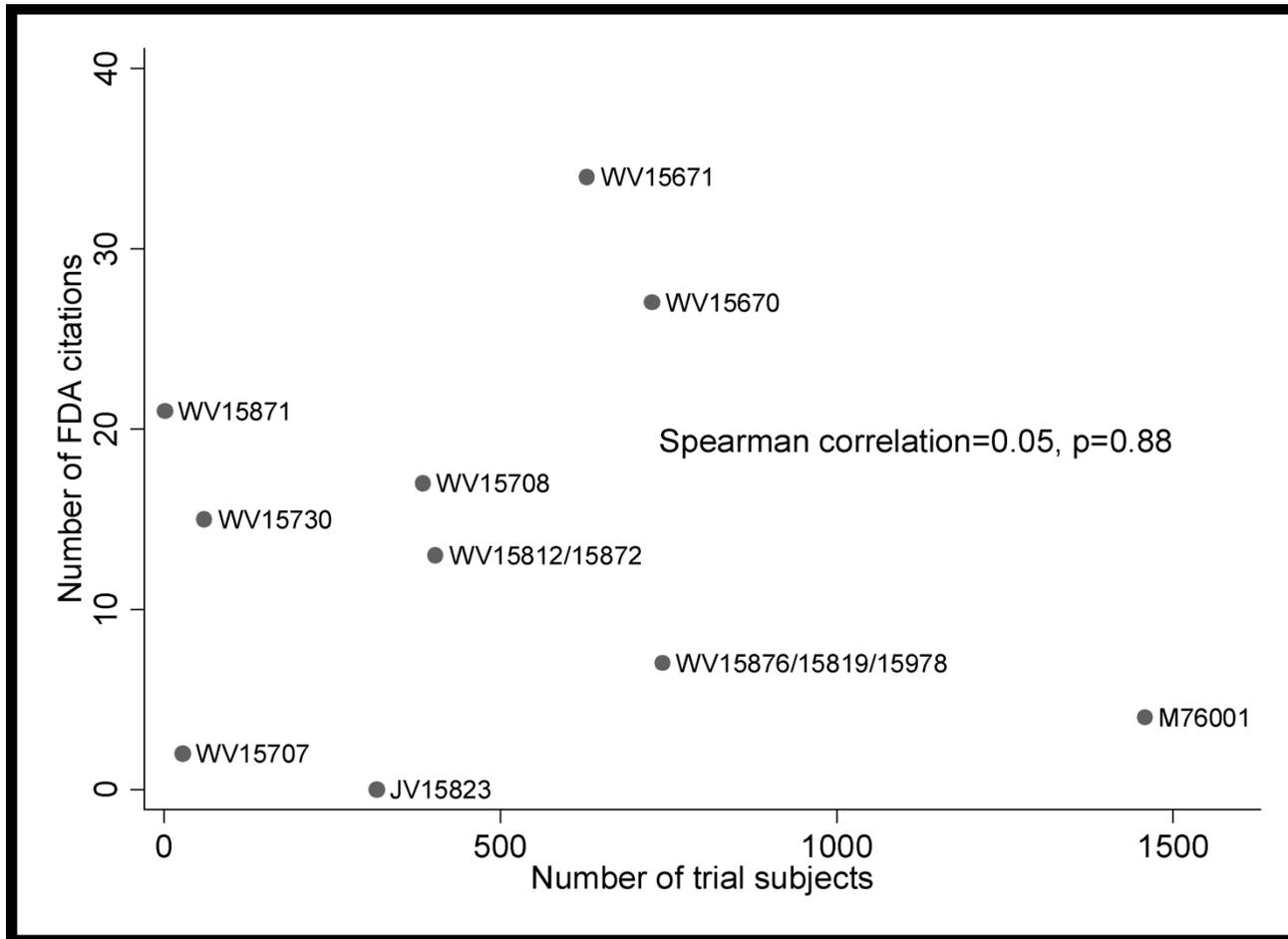
# FDA Medical Officer Report (MOR)

(completed 12 Oct 1999)

In response to FDA's request, the applicant provided a summary of diary card dispensing in the 8/6/99 submission. It became apparent that instructions on when to start a second diary card were not uniformly followed in WV15670, WV15671, and WV15730 trials. There were examples of patients who had alleviated symptoms yet also received a second diary card. Conversely, there were also examples of patients who did not alleviate all symptoms but did not receive a second diary card. Thus the second diary card was used inconsistently which is viewed as a flaw of these trials. The lack of consistency in collecting symptom information after alleviation precluded a complete documentation of symptom fluctuation. Also missing second diary cards in subjects who had not alleviated symptoms were responsible for the majority of censored data which may have potentially influenced the results of efficacy analysis. In order to address the impact of censoring, the applicant performed several sensitivity analyses which will be summarized in the Integrated Summary of Efficacy.

# FDA core data for NDA: trial citation density vs size

(courtesy Mark Jones)



# Conclusions

- Do not trust and verify to death
- Whither medical journals?
- Whither research synthesis?
- Whither regulation?
- New methods, new concepts, ethics needed.