Disease Registry vs RCT Outcomes: Sexual Medicine Opportunities and Challenges

Presenter: Raymond C. Rosen, PhD
New England Research Institutes
Disease registry provides “real world” outcomes vs. scientific rigor in RCT.

Registry has fewer exclusion criteria and more representative clinical population

More treatment options and longer period of treatment in disease registry vs RCT

QOL outcomes important in both.

Relatively few well-designed disease registries in sexual medicine
Largest, multinational disease registry in sexual medicine to date.

1000 male patients with diagnosed hypogonadism in 25 European sites

80% of patients treated with TRT for up to 3 years.

Primary endpoints – prostate and cardiovascular safety

Secondary endpoints – sexual function/QOL

Funded by Bayer AG
Clinical Sites

101 University of Florence
102 University Hospital Halle
103 VU Medical Centre
104 Erasmus MC Rotterdam
105 Karolinska University Hospital
106 Manchester Royal Infirmary
107 Private Practice of Urology/Andrology: Dr. Porst
108 Barnsley Hospital NHS Foundation Trust
109 Victoria Royal Infirmary
110 Sapienza University of Rome
111 Royal Free Hampstead NHS
112 Carlos Haya University Hospital
113 Holly Cottage Clinic
114 Urohälsan i Skövde
115 University of Parma
116 Hospital Virgen del Rocio
117 Ospedali Riuniti - Ancona
118 Segeberger Kliniken
119 Hospital Universitario 12 Octubre
120 Hospital Universitario Puerta de Hierro-Majadahonda
121 Andros Men’s Health Institutes

### Inclusion Criteria
- Male patients with a current diagnosis of HG
- Aged 18 years and older (maximum: 150 men <50y)
- Informed consent

### Exclusion Criteria
- Any previous treatment with testosterone therapy for any reason
- History of certain cancers or high-grade prostatic intraepithelial neoplasia
- Prior radical prostatectomy
- Life expectancy shorter than 24 months
- Current major psychiatric disorders or drug/alcohol abuse
- Gender dysphoria or sexual reassignment (e.g. transsexualism)
- Enrolled in any interventional clinical trial within the past 30 days
- Planned relocation outside Site region within 24 months
Measurement and Visit Schedule

**Baseline**
- Medical history
  - Clinical BPH and ED, low libido
- Physical exam
  - DRE per local standard
- Medications
  - Testosterone
  - PDE-5i
  - 5-alpha-reductase inhibitors (5ARIs)
  - Alpha-blockers (AB)
- Blood sample (local and central)
  - Serum PSA, LH, T, SHBG
- Patient questionnaire
  - IIEF (ED)
  - AUASI (LUTS, Voiding, Storage)
  - Patient-reported history/symptoms

**Follow-up**
- Medical history update
- Physical exam
- Medications
- Blood sample (local and central)
- Patient questionnaire
RHYME Prostate Health and Clinical Endpoints Committee.
Roehrborn (Chair), Schroder, Cunningham, Jackson

Prostate Biopsy Adjudication
- Clinical Site completes prostate biopsy form
- Clinical Site provides additional documentation (e.g., pathology report, TRUS)
- PHCEC reviews biopsy documentation and reports its final assessment

Mortality Adjudication
- Similar process to Prostate Adjudication
- Purpose: To assess cause of death
- Modeled after the European Randomized Study of Screening for Prostate Cancer (ERSPC) algorithm

RHYME Patient Disposition and TRT Use

Patients enrolled into the Registry from 2005 to 2011

7 patients found ineligible post-consent

1006

Non-Testosterone Users

249

- Baseline mean testosterone: 9.4 nmol/L
- Follow-up mean testosterone: 11.3 nmol/L

Testosterone Users

750

Patterns of Use:
- 529 consistent users
- 132 discontinuers
- 57 late starters
- 32 in-between visit users

Administration Routes:
- 68% topical gels
- 31% injectable
- 2% oral

Baseline mean testosterone: 8.3 nmol/L
Follow-up mean testosterone: 15.4 nmol/L
RHYME PSA Levels at Baseline

IPSS to 36 Months in Treated vs Untreated Patients

Prostate Cancer Incidence and TRT

TOTAL QOL and Sexual Symptom Scores

Adjusted AMS Total Score

Adjusted AMS Sexual Score

[UNPUBLISHED RHYME DATA]
### Incidence of Cardiovascular (CV) Events

<table>
<thead>
<tr>
<th>Per 100,000 PY</th>
<th>On T N=750</th>
<th>Not on T N=249</th>
<th>Total N=999</th>
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</thead>
<tbody>
<tr>
<td><strong>Overall populations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset CV event (n)</td>
<td>32</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Person-years</td>
<td>2162.2</td>
<td>531.0</td>
<td>2693.2</td>
</tr>
<tr>
<td>CV Incidence rate</td>
<td>1480.0</td>
<td>1694.7</td>
<td>1522.3</td>
</tr>
<tr>
<td><strong>&lt;60 yrs populations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset CV event (n)</td>
<td>7</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Person-years</td>
<td>1055.6</td>
<td>168.9</td>
<td>1224.4</td>
</tr>
<tr>
<td>Incidence rate</td>
<td>663.1</td>
<td>1184.3</td>
<td>735.0</td>
</tr>
<tr>
<td><strong>≥60 yrs populations</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Onset CV event (n)</td>
<td>25</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>Person-years</td>
<td>1106.6</td>
<td>362.2</td>
<td>1468.8</td>
</tr>
<tr>
<td>Incidence rate</td>
<td>2259.2</td>
<td>1932.7</td>
<td>2178.7</td>
</tr>
</tbody>
</table>

• Sustained improvements over time in QOL and Sexual Function Scores, including IIEF and IPSS changes.

• Prostate cancer and elevated PSA rates were not higher in men receiving up to 3 years of TRT compared to untreated men or population controls.

• No effects of TRT use was observed in higher Gleason scores or other prostate cancer parameters.

• Cardiovascular outcomes were comparable in TRT users and non-users up to 3 years of follow up.

• Taken together, RHYME supports sustained benefits and overall safety of TRT use in hypogonadal men.

• Longer studies in other patients groups are needed.
HSDD Registry for Women

- Multi-center, large scale patient registry of women with diagnosed HSDD.
- 34 clinical sites throughout the US
- 1500+ women with HSDD (1000 pre-; 500 post-menopausal)
- Comprehensive data on medical, psychosocial and sexual function variables.
- First large-scale patient registry study in sexual medicine.

Site Investigators in the HSDD Registry (2008-2012)

Stanley Althof, PhD
Peter Auerbach, MD
Candace Brown, PharmD
James Clark, MD
Mario Cohen, MD
Gregg Coodley, MD
Nupar Dashottar, MD
Deborah Davenport, MD
Brenda Dawley, MD
Leonard Derogatis, PhD
Jenelle Foote, MD
Peter Gagianas, MD
Irwin Goldstein, MD
Michael Graham, MD
Lester Ho, MD
Susan Kellogg-Spadt, PhD
Michael Krychman, MD
Ginger Kubala, MD
Andrew Lewis, MD
Abraham Lichtmacher, MD
John McGettigan, MD
Anjali Mehta, MD
Adine Regan, MD
Jack Ritter, MD
Robert Rosen, MD
Gerrit Schipper, MD
Mitul Shah, MD
Gerald Sigman, MD
James Simon, MD
Suzanne Trupin, MD
Scott Walker, MD
Harry Watters, DO

HSDD Registry for Women: Summary of Design and Measures

Baseline
In-person clinic visit
- Patient Screening (includes the Decreased Sexual Desire Screener)
- Medical History Form
- Patient Self-administered Form
  
  Includes assessments of:
  - HSDD onset and help-seeking
  - Female sexual function, e.g.:
    - Female Sexual Function Index (FSFI)
    - Female Sexual Distress Scale Revised Question 13
    - Sexual Desire Distress
    - Frequency of sexual activity
    - Relationship status & satisfaction
    - Quality of life (SF-36)
    - Patient Health Questionnaire-9 (PHQ-9)
- Physical health conditions
- Mental health conditions
- Health care use

Three-monthly follow-up
In-person or remote (web, telephone, or postal)
- Patient Self-administered Form
  
  Includes assessments of:
  - Patient global impressions of HSDD
  - Frequency of sexual activity
  - Relationship status and satisfaction update
  - Health care resource use
  - HSDD treatments and satisfaction
  - Subjective global health
  - HSDD distress

Six-monthly follow-up
In-person or remote (web, telephone, or postal)
- Medical History Form
- Patient Self-administered Form
  
  Includes assessments of:
  - Patient global impressions of HSDD
  - Female sexual function:
    - FSFI
  - Female Sexual Distress Scale Revised Question 13
  - Sexual Desire Distress
  - Frequency of sexual activity
  - Relationship status & satisfaction
  - Quality of life (SF-12)
  - PHQ-9
  - Physical health conditions
  - Mental health conditions
  - Health care use
Hormonal Contraceptive Use

*Similar to findings from national data (CDC, 2002 data) overall and by age

<table>
<thead>
<tr>
<th>Current use of any hormonal contraceptive</th>
<th>Total N=1088</th>
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<tbody>
<tr>
<td>Yes</td>
<td>305 (28.0)</td>
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<tr>
<td>No</td>
<td>783 (72.0)</td>
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<table>
<thead>
<tr>
<th>Current use of oral contraceptives*</th>
<th>Total N=1088</th>
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<tbody>
<tr>
<td>Yes</td>
<td>196 (18.0)</td>
</tr>
<tr>
<td>No</td>
<td>891 (81.9)</td>
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<table>
<thead>
<tr>
<th>Oral contraceptive use</th>
<th>Total N=1088</th>
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</thead>
<tbody>
<tr>
<td>Never OC user</td>
<td>133 (12.2)</td>
</tr>
<tr>
<td>Past OC user &lt;6 yrs</td>
<td>378 (34.8)</td>
</tr>
<tr>
<td>Past OC user 6+ yrs</td>
<td>380 (35.0)</td>
</tr>
<tr>
<td>Current OC user &lt;6 yrs</td>
<td>43 (4.0)</td>
</tr>
<tr>
<td>Current OC user 6+ yrs</td>
<td>153 (14.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current any hormonal contraceptive use</th>
<th>Mild-to-moderate (N=175)</th>
<th>Moderate-to-severe (N=628)</th>
<th>Severe-to-very severe (N=284)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Yes</td>
<td>53 (30.3)</td>
<td>186 (29.6)</td>
<td>66 (23.2)</td>
<td>0.11</td>
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<tr>
<td>No</td>
<td>122 (69.7)</td>
<td>442 (70.4)</td>
<td>218 (76.8)</td>
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</table>

<table>
<thead>
<tr>
<th>Current oral contraceptive use</th>
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<th>0.08</th>
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<tbody>
<tr>
<td>Yes</td>
<td>34 (19.4)</td>
<td>124 (19.7)</td>
<td>39 (13.7)</td>
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</tr>
<tr>
<td>No</td>
<td>141 (80.6)</td>
<td>504 (80.3)</td>
<td>245 (86.3)</td>
<td></td>
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</table>

<table>
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<tr>
<th>Oral contraceptive use</th>
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<th></th>
<th>0.17</th>
</tr>
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<tbody>
<tr>
<td>Never OC user</td>
<td>27 (15.4)</td>
<td>72 (11.5)</td>
<td>34 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Past OC user &lt;6 yrs</td>
<td>51 (29.1)</td>
<td>225 (35.8)</td>
<td>102 (35.9)</td>
<td></td>
</tr>
<tr>
<td>Past OC user &gt;6 yrs</td>
<td>64 (36.6)</td>
<td>207 (33.3)</td>
<td>109 (38.4)</td>
<td></td>
</tr>
<tr>
<td>Current OC user &lt;6 yrs</td>
<td>7 (4.0)</td>
<td>25 (4.0)</td>
<td>11 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Current OC user &gt;6 yrs</td>
<td>26 (14.9)</td>
<td>99 (15.8)</td>
<td>28 (9.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>My body is sexually appealing</th>
<th>Pre-Menopausal (N = 1,074)</th>
<th>Post-Menopausal (N = 467)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disagree</td>
<td>44.88%</td>
<td>46.47%</td>
</tr>
<tr>
<td>Neither agree nor disagree</td>
<td>18.06%</td>
<td>20.34%</td>
</tr>
<tr>
<td>Agree</td>
<td>37.06%</td>
<td>33.19%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I like the way I look without my clothes</th>
<th>Pre-Menopausal (N = 1,076)</th>
<th>Post-Menopausal (N = 467)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disagree</td>
<td>34.76%</td>
<td>27.62%</td>
</tr>
<tr>
<td>Neither agree nor disagree</td>
<td>12.45%</td>
<td>16.06%</td>
</tr>
<tr>
<td>Agree</td>
<td>52.79%</td>
<td>56.32%</td>
</tr>
</tbody>
</table>
HSDD in women is prevalent and distressing in a substantial proportion of pre- and post-menopausal women.

Little is known about the natural history, course of progression, treatments, comorbidities and outcomes in women with generalized HSDD.

A large, multi-center patient registry was established by NERI to study these issues.

The HSDD Registry was discontinued in 2012 with Boehringer Ingelheim’s opting out as sponsor.
Multi-center disease registries have important benefits compared to clinical trials.

Relatively few registries in sexual medicine compared to RCT’s.

RHYME – Largest HG registry to date.

The HSDD Registry.

Need for more large, well-controlled sexual medicine registries in the future.
Thank you.

Contact:

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rrosen@neriscience.com